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CERIUM AMIDE ENOLATES AND LITHIUM NAPHTHALENIDE IN ORGANIC SYNTHESIS AND SYNTHESES OF KEY INTERMEDIATES TOWARDS FORSKOLIN

by

XIAO SHANG

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1995

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Xiao Shang

Xiao Shang

Permanent Address:
Pizhou City, Jiangsu
China

Date: Sept. 27, 1995

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled CERIUM AMIDE ENOLATES AND LITHIUM NAPHTHALENIDE IN ORGANIC SYNTHESIS, AND SYNTHESES OF KEY INTERMEDIATES TOWARDS FORSKOLIN submitted by XIAO SHANG in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

H.J. Liu
Supervisor

K.R. Kopecky

D.L.J. Clive

R.E.D. McClung

E.E. Knaus

T.G. Back
External Examiner

Date: Sept. 25, 1995

Dedicated To My Parents

Abstract

The first chapter of this thesis describes the preparation of cerium amide enolates and their reactions with aldehydes, ketones and α,β-unsaturated ketones. The cerium enolates of *N,N*-dimethylacetamide and *N,N*-dimethylpropionamide were found to undergo addition reactions with aldehydes and ketones effectively. With certain sterically hindered or highly enolizable ketones, the cerium enolates delivered higher yields of the products than the corresponding lithium enolates. With conjugated enones, the cerium enolate **8** showed higher product selectivity for the 1,2-adducts over the 1,4-adducts than the corresponding lithium enolate.

The second chapter presents the syntheses of some advanced intermediates towards forskolin. Using an intermolecular Diels-Alder cycloaddition approach, compound **203** was prepared in good yield. This compound possesses all the carbon atoms needed for the A-B ring moiety of forskolin with suitable functional groups well positioned for further elaboration. After reducing the enone to a secondary alcohol, removing the silyl group and forming an acetal group with the resulting diol, the ester group was reduced and the resulting neopentyl alcohol **213** converted to the mesylate **218**. Reduction of **218** gave the unexpected diene **219**, which was readily converted to the endoperoxide lactone **131**, a key intermediate in Corey's synthetic scheme. The preparation of enone **156**, which appeared in Nicolaou's synthetic scheme, was also accomplished. Alcohol **213** was deoxygenated *via* the corresponding *N,N,N',N'*-tetramethylphosphorodiamidate to give **215**. Numerous attempts to prepare **156** by allylic oxidation of the double bond were fruitless. An indirect route was hence explored. Epoxidation of **215** followed by phenylselenide

attack on the resulting epoxide gave β-phenylselenenyl alcohol. Oxidative elimination with hydrogen peroxide failed to deliver the desired allylic alcohol **238**. This oxidative elimination, a subsequent oxidation of the allylic alcohol to enone **216** and epimerization of **216** into **156** was achieved with a one-pot procedure, using CrO_3-pyridine as the oxidant, followed by treatment with methanolic NaOH.

The third chapter details a facile procedure for the reduction of *N,N,N',N'*-tetramethylphosphorodiamidates, which has been frequently used for deoxygenation of alcohols and ketones. Instead of using lithium metal and liquid ammonia or an alkylamine, lithium naphthalenide was used as a convenient source of "free" electrons. A stock solution of this reducing agent could be easily prepared by mixing lithium metal and naphthalene in THF, and stored in a refrigerator for weeks without substantial loss of reactivity. A number of functional groups were found to be compatible with the reduction conditions applied.

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List of Abbreviations

Ac	Acetyl
acac	acetylacetonate
AIBN	Azobisisobutyronitrile
AMP	Adenosine Monophosphate
ap	anti-phase
APT	Attached Proton Test
BB	Broad Band
Bn	Benzyl
BOMO	Benzyloxymethoxy
br	broad
Bu	butyl
c	cyclo
CIMS	Chemical Ionization Mass Spectrometry
CSA	Camphorsulfonic Acid
d	doublet
DBU	1,5-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEP	Diethyl Phosphate
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMPADC	*N,N*-Dimethylphosphoramidic Dichloride

DMSO	Dimethyl sulfoxide
EEO	Ethoxyethoxy
eq	equivalent
Eq.	Equation
Et	Ethyl
FTIR	Fourier Transform Infrared Spectroscopy
hr	hour
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
INOC	Intramolecular Nitrile Oxide Cycloaddition
IR	Infrared Spectroscopy
LA	Lewis Acid
LBTMSA	Lithium Bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamide
LN	Lithium Naphthalenide
m	multiplet
md	medium
MCPBA	*m*-Chloroperoxybenzoic Acid
Me	Methyl
min	minute
MOM	Methoxymethyl
mp	melting point
MS	Mass Spectrometry
Ms	Mesyl
NBS	*N*-Bromosuccinamide
NMR	Nuclear Magnetic Resonance
N-PSP	*N*-Phenylselenophthalimide

NOE	Nuclear Overhauser Enhancement
p	para
p	phase
p-TsOH	p-Toluenesulfonic Acid
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
PLE	Pig Liver Esterase
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-Toluenesulfonate
Pr	Propyl
Py	Pyridine
q	quartet
r.t.	room temperature
s	singlet
SET	Single Electron Transfer
st	strong
t	tertiary
t	triplet
t.l.c.	thin-layer chromatography
TBAF	Tetrabutylammonium Fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDMSCl	*t*-Butyldimethylsilyl Chloride
TBDPS	*t*-Butyldiphenylsilyl
TBDPSCl	*t*-Butyldiphenylsilyl Chloride
Tf	Triflate
THF	Tetrahydrofuran

THP	Tetrahydropyranyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMPDA	*N,N,N',N'*-Tetramethylphosphorodiamidate
TMS	Tetramethylsilane or Trimethylsilyl
w	weak

Chapter One

Addition of Cerium Amide Enolates to Carbonyl Compounds

Introduction

The nucleophilic addition of organometallic reagents to carbonyl compounds is one of the most commonly used and the most versatile reactions in synthetic organic chemistry.[1] The most common counterions are probably the group IA metals, like sodium, lithium or potassium, or those "MgX" in Grignard reagents. Despite their broad applicabilities, certain side reactions, such as enolization, conjugate addition, condensation and reduction, are often associated with these reagents and it is always desirable to eliminate or suppress these reactions and improve the yield and selectivity for the desired ones.

In the past decade or so, an increasing number of reports on the application of cerium(III) reagents appeared in the literature. In 1981, Imamoto *et al.* reported for the first time the preparation of tertiary alcohols from ketones in excellent yields by using organocerium reagents $RCeX_2$ prepared *in situ* by oxidative insertion of cerium (in the form of cerium amalgam) to allylic or benzylic iodides.[2] They discovered that this one-step Barbier-type reaction was very chemoselective. Ketones reacted smoothly, while other functional groups, such as ester, nitrile and aryl bromide reacted at much slower rates. Another characteristic of this reagent was its tendency towards 1,2-addition. With 1,3-diphenylpropanone, only the 1,2-adduct was isolated. One year later, they reported a new, more general method of preparing the cerium reagents. Transmetallation of alkyllithium at -65 °C with cerium iodide, which was prepared by reacting cerium metal with iodine in THF from 0 °C to 25 °C, gave the corresponding alkylcerium reagent.[3] At low temperature, these reagents demonstrated similar behaviors as those prepared by oxidative insertion of

cerium metal to allylic or benzylic iodides, as in the case of *p*-iodoacetophenone (Table 1-1).

Table 1-1 The reaction of CeI_3-RLi or RLi with ketones

Reagent	Ketone	Product	Yield (%)
n-BuLi-CeI_3	Bn_2CO	$Bn_2C(OH)Bu$-*n*	98
n-BuLi	Bn_2CO	$Bn_2C(OH)Bu$-*n*	36
n-BuLi-CeI_3	*p*-IPhCOMe	*p*-IPhC(OH)MeBu-*n*	99
n-BuLi	*p*-IPhCOMe	*p*-IPhC(OH)MeBu-*n*	0
s-BuLi-CeI_3	PhCOMe	PhC(OH)MeBu-*s*	98
s-BuLi	PhCOMe	PhC(OH)MeBu-*s*	53

Another characteristic of the reagents lies in their reactions with highly enolizable ketones, like 1,3-diphenyl-2-propanone. While the lithium reagent gave a low yield of the desired product and the recovery of starting material due to enolization, the cerium reagent gave an excellent yield of the desired adduct.

In 1984, Imamoto *et al.* examined the use of commercially available lanthanoid chlorides ($CeCl_3 \bullet 7H_2O$, $LaCl_3 \bullet 7H_2O$, $NdCl_3 \bullet 6H_2O$, $PrCl_3 \bullet 7H_2O$, $SmCl_3 \bullet 6H_2O$, $YbCl_3 \bullet 6H_2O$) in place of CeI_3.[4,5] The anhydrous salts were prepared by drying the hydrates in *vacuo* at 140 °C for 2 hr. Vigorous stirring of the dried $LnCl_3$ in THF at room temperature followed by the addition of alkyllithium at -78°C and subsequent stirring would provide the transmetallated reagent $RLnCl_2$. They discovered that, while excellent results were obtained for cerium chloride, lanthanum chloride, neodymium chloride and ytterbium chloride, lower yields were observed for praseodymium chloride and samarium chloride. Considering the ready availability, moderate price and the relative ease to dry it, cerium chloride seemed to be the best choice.

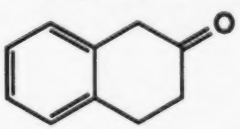
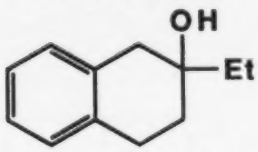
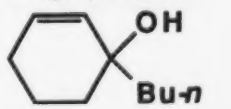
The observed high reactivity towards carbonyl compounds, less tendency to cause enolization of the substrate and propensity for 1,2-addition were ascribed to the higher oxophilicity and lower basicity of these cerium reagents.

In subsequent publications, Imamoto and co-workers reported that the organocerium reagents could also be prepared from the corresponding Grignard reagents,[6,7] alkenyl, aryl[5] or alkynyl organometallic reagents. Compared with their precursors before transmetallation, these cerium reagents all demonstrated the same tendencies in their nucleophilic attacks on carbonyl compounds, as those derived from RLi - $CeCl_3$.

Treatment of Grignard reagents with $CeCl_3$ helped to suppress the side-reactions associated with them due to their high basicity or tendency to act as hydride reducing agents at elevated temperatures.[8] Selected examples are given in Table 1-2. The Grignard reagent MeMgBr failed to react with hindered ketones like 3,3-diethyl-2-pentanone, while the cerium reagent offered the desired products in 95% yield (Entries 1 and 2). With β-tetralone, the α-proton is very acidic. Reaction with EtMgCl itself gave only 8% of the adduct due to enolization. The yield was increased to 76% after transmetallation with $CeCl_3$ (Entries 3 and 4). With 1,3-diphenyl-2-propanone, another highly enolizable ketone, the yield was again higher for the cerium reagent than for the simple Grignard reagent *n*-BuMgBr (Entries 5 and 6). Furthermore, contrary to the *t*-butyl Grignard reagent which acted as a base and reducing agent rather than a nucleophile, the *t*-butylcerium reagent added to 1,3-diphenyl-2-propanone to give the adduct in 67% yield (Entries 7 and 8). With α,β-unsaturated ketones, the cerium reagents again showed strong preference for 1,2-addition over 1,4-addition, while the Grignard reagents usually gave mixtures of 1,2- and 1,4-adducts (Entries 9 and 10).[9]

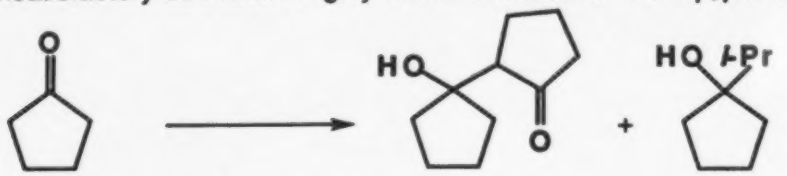
Another advantage of the $RMgX\text{-}CeCl_3$ combination lies in the temperature that the reactions could be run at. It was noted that the cerium chloride promoted Grignard addition to ketones could be performed at 0 °C instead of -78 °C required for organolithium derived cerium reagents. Enolization and subsequent aldol condensation, or hydride reduction were suppressed by the use of cerium chloride (Eq. 1-1 and 1-2).

Table 1-2: Reactions of cerium reagents derived from Grignard reagents

Entry	Ketone	Reagent	Product	Yield (%)
1	Et_3CCOMe	MeMgBr	$Et_3CC(OH)Me_2$	0
2	Et_3CCOMe	$MeMgBr\text{-}CeCl_3$	$Et_3CC(OH)Me_2$	95
3		EtMgCl		8
4	"	$EtMgCl\text{-}CeCl_3$	"	76
5	Bn_2CO	*n*-BuMgBr	$Bn_2C(OH)Bu\text{-}n$	10
6	Bn_2CO	$n\text{-}BuMgBr\text{-}CeCl_3$	$Bn_2C(OH)Bu\text{-}n$	96
7	Bn_2CO	*t*-BuMgBr	$Bn_2C(OH)Bu\text{-}t$	0
8	Bn_2CO	$t\text{-}BuMgBr\text{-}CeCl_3$	$Bn_2C(OH)Bu\text{-}t$	65
9		*n*-BuMgBr		48
10	"	$n\text{-}BuMgBr\text{-}CeCl_3$	"	98

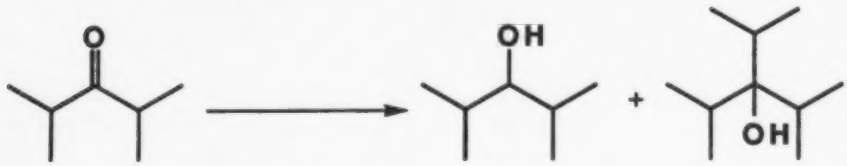
The vinylcerium reagent could be prepared in the same manner. It was successfully incorporated into their synthesis of a chiral pheromone by

Tsuchihashi *et al.* (Eq. 1-3).[10] The use of organolithium or Grignard analogs was unsatisfactory due to the highly enolizable nature of the β,γ-enone.



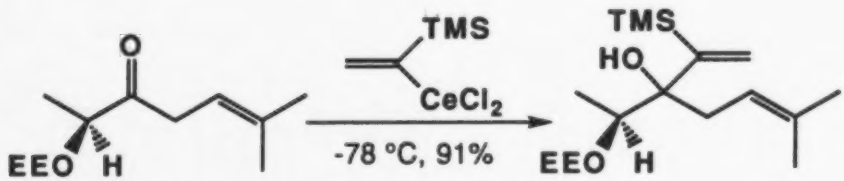
(1-1)

i-PrMgCl	80%	3%
i-PrMgCl-$CeCl_3$	trace	72%



(1-2)

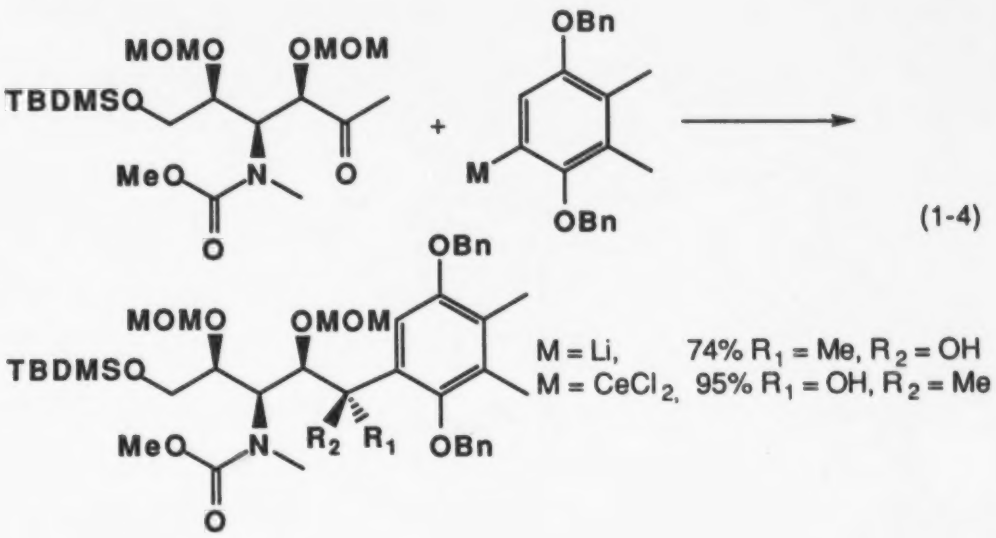
i-PrMgCl	58%	3%
i-PrMgCl-$CeCl_3$	31%	52%



(1-3)

Aryllithium reagents could also undergo transmetallation reactions with $CeCl_3$. Sometimes the stereochemical path of the reaction could also be altered, due to the different coordination patterns with the functional groups present in the substrate, as evidenced by the following example. Terashima *et al.*[11] discovered that the lithium reagent gave the wrong stereochemistry (Eq. 1-4) during their construction of the DEF-ring of nogalamycin, an antitumor antibiotic. The use of the corresponding cerium reagent gave the product with the right stereochemistry at the newly formed stereogenic center. The results were rationalized by the assumption that the cerium atom coordinates strongly

with the adjacent ether group in the substrate, while lithium coordinate preferably with the solvent THF molecules.



Alkynyllithium reagents are much weaker bases compared with alkyllithium or alkenyllithium reagents. Nevertheless, substantial portions of those highly enolizable substrates underwent enolization reactions when treated with alkynyllithium reagents. These problems could be alleviated or solved by transmetallation with $CeCl_3$ (Table 1-3). Another benefit with the cerium reagents was their chemoselectivity, as evidenced in the reaction with 2,4'-dibromoacetophenone. No substitution of the bromide at either position was observed with the cerium reagent, while the lithium reagent gave no simple addition product at all, due to the substitution reactions.

The pronounced nucleophilicity of organocerium reagents prompted Imamoto *et al.* to study the cerium mediated ketone enolate addition reactions with carbonyl compounds.[12] The lithium enolates, generated with lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LBTMSA), were

treated with anhydrous cerium chloride at -78 °C. The so generated cerium enolates were allowed to react with carbonyl compounds at the same temperature for 0.5 - 3 hr. Excellent yields were obtained for the cerium enolates, comparing favorably with those for the lithium enolates. It was postulated that the cerium ion likely played a more effective role than the lithium ion in the chelating process with the intermediate leading to the aldol adduct, suppressing retro-aldol and/or proton exchange reactions. However, similar stereoselectivity was observed for both reagents, indicating the same geometry for both the lithium and cerium enolates. Selected examples are given in Table 1-4.

Table 1-3: Comparison of the reactivity of alkynyllithium and cerium reagents

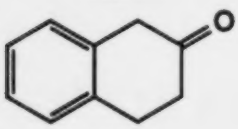
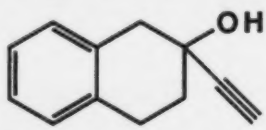
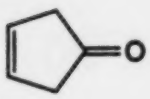
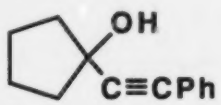
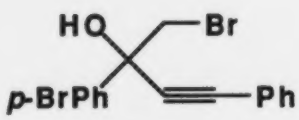
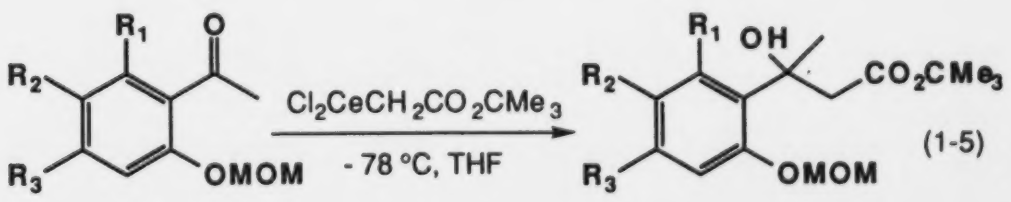
Ketone	Reagent	Product	Yield (%)
Bn_2CO	$HC{\equiv}CCeCl_2$	$Bn_2C(OH)C{\equiv}CH$	95
Bn_2CO	$HC{\equiv}CLi$	$Bn_2C(OH)C{\equiv}CH$	60
	$HC{\equiv}CCeCl_2$		89
"	$HC{\equiv}CLi$	"	10
	$PhC{\equiv}CCeCl_2$		89
"	$PhC{\equiv}CLi$	"	30
p-$BrPhCOCH_2Br$	$PhC{\equiv}CCeCl_2$		95
p-$BrPhCOCH_2Br$	$PhC{\equiv}CLi$	"	0

Table 1-4: Comparison of reactions of lithium and cerium ketone enolates with carbonyl compounds

Enolized Ketone	Substrate	Reagent	Yield %
PhCOEt	Cyclohexanone	LDA-$CeCl_3$	79
PhCOEt	Cyclohexanone	LDA	28
PhCOEt	Cyclopentanone	LDA-$CeCl_3$	45
PhCOEt	Cyclopentanone	LDA	5
PhCOEt	Mesitaldehyde	LDA-$CeCl_3$	93
PhCOEt	Mesitaldehyde	LDA	63
PhCOMe	*p*-Chloroacetophenone	LDA-$CeCl_3$	60
PhCOMe	*p*-Chloroacetophenone	LDA	26

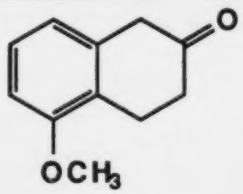
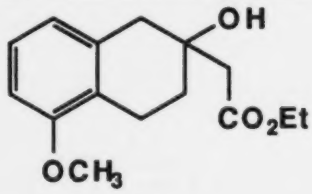
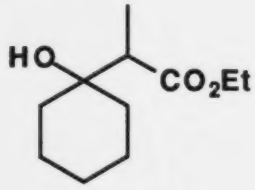
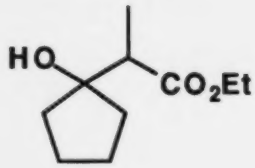
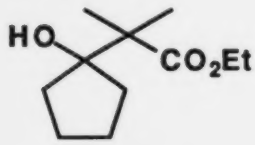
Cerium ester enolates were first utilized by Imamoto *et al.* in the Reformastky-type of reactions.[5] The α-haloesters were treated with cerium amalgam in the presence of carbonyl compounds. Satisfactory to excellent yields were obtained. One year later, Nagasawa *et al.*[13] reported the use of cerium enolate $Cl_2CeCH_2COOCMe_3$ in a reaction with acetophenone derivatives to furnish β-hydroxy esters in excellent yields (Eq. 1-5). This enolate was generated by transmetallation of the lithium enolate with $CeCl_3$. In comparison, the use of the lithium enolate of *t*-butyl acetate or the Reformatsky type reactions under a wide variety of conditions afforded only recovered starting materials.

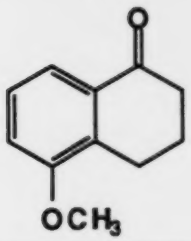
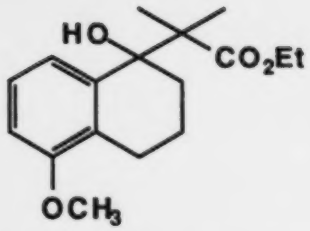


(1-5)

The addition of cerium ester enolates to different ketones was extensively studied in our laboratory.[14,15] These cerium enolates were generated by transmetallation of the corresponding lithium enolates with anhydrous $CeCl_3$ at -78 °C. Excellent yields were obtained from the reactions of these enolates with ketones (Table 1-5). With 5-methoxy-β-tetralone, a highly enolizable ketone, the adduct was produced in 92%. Obviously, the commonly seen side reactions, like retro-aldol, enolization, self-condensation between the substrates, were suppressed.

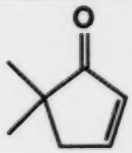
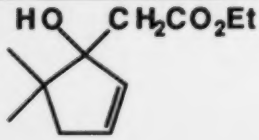
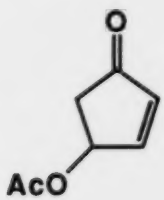
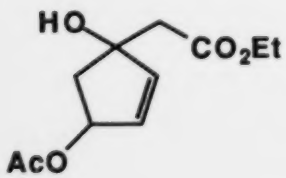
Table 1-5: Reaction of ester cerium enolates with ketones

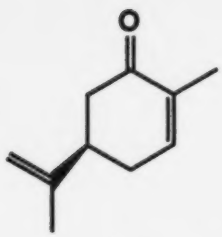
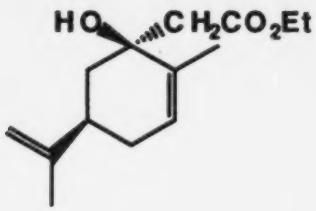
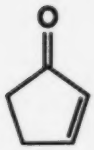
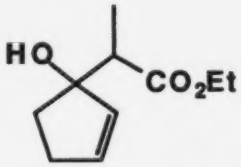
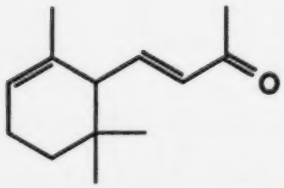
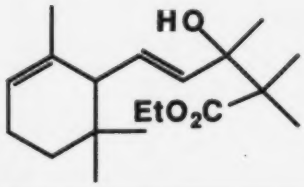
Ester	Substrate	Product	Yield (%)
CH_3CO_2Et			92
$EtCO_2Et$			94
$EtCO_2Et$			97
Me_2CHCO_2Et			97

Me_2CHCO_2Et			97

With α,β-unsaturated ketones, cerium ester enolates showed a high preference for 1,2-addition with excellent yields (Table 1-6). With 5,5-dimethyl-2-cyclopenten-1-one, a hindered ketone, 97% yield was obtained with the cerium enolate of ethyl acetate. This compared favorably with the 60% yield obtained with the corresponding lithium enolate. The tertiary allylic alcohols produced this way could be oxidized with pyridinium chlorochromate (PCC) to afford α,β-unsaturated ketones through 1,3-keto transposition. This methodology was successfully incorporated into the synthesis towards pentalenolactone.[14]

Table 1-6: Reaction of ester cerium enolates with α,β-unsaturated ketones

Ester	Substrate	Product	Yield (%)
CH_3CO_2Et			97[a]
CH_3CO_2Et			98

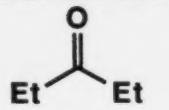
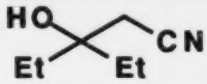
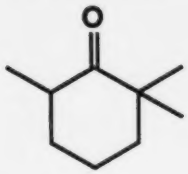
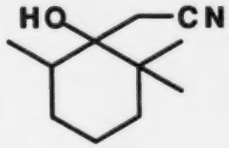
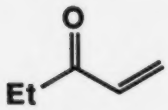
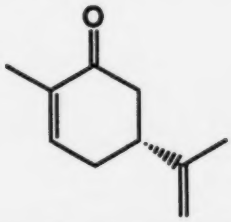
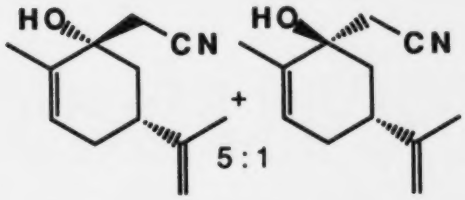
CH_3CO_2Et			100
$EtCO_2Et$			96
Me_2CHCO_2Et			100

[a]The yield for the corresponding lithium enolate was 60%.

Later, the methodology was extended to nitrile enolates in our group.[16,17] Good to excellent yields were obtained with the cerium enolate of acetonitrile. It reacted with sterically hindered ketones, like 2,2,6-trimethylcyclohexanone, to give higher yields than the lithium enolate. With α,β-unsaturated ketones, only the 1,2-adducts were observed and isolated (Table 1-7). Surprisingly, the reactions with cerium acetonitrile were slow at -78 °C. It was necessary to bring the temperature to room temperature to complete the reaction. Derivatives of substituted acetonitriles were much less reactive. The reaction of dichlorocerio propionitrile (2 eq.) with diethyl ketone gave the expected addition product in 62% yield along with recovered starting material after prolonged treatment at room temperature. In the case of isobutyronitrile, the cerium reagent was found to be unreactive towards diethyl ketone at room temperature.

At higher temperature (refluxing THF), a complex mixture was produced, most likely due to decomposition of the reagent.

Table 1-7: Addition of cerium enolate of acetonitrile to ketones.

Substrate	Product	Yield (%)
		100
		88[a]
		82[b]
		100

[a]The yield with lithioacetonitrile was 60%.
[b]The yield with lithioacetonitrile was 53%.

The addition of amide enolates to carbonyl compounds has been very useful in synthetic organic chemistry. Heathcock and co-workers extensively studied the 1,2- and 1,4-additions of the lithium enolates of oxo- and thio-amides and lactams to a series of α,β-unsaturated ketones.[18] They discovered the following:

(1) Bulkier enolates had greater propensity for 1,4-addition. Smaller amides like *N,N*-dimethylacetamide gave predominately 1,2-adducts, while larger ones like *N,N*-dimethylisobutyramide gave mainly 1,4-adducts.

(2). The 1,4-adducts were the thermodynamically more stable products. Upon standing at room temperature for a period of time, the initially formed 1,2-adducts could be converted to the 1,4-adducts under the reaction conditions.

(3) The lactam enolates (*E*-enolates) showed a greater propensity for 1,2-addition than did acyclic *Z*-enolates.

(4) Increasing the size of the alkyl group attached to the carbonyl group (the carbonyl ligand) decreased the preference for 1,2-addition.

(5) Enlarging the alkyl group at the β-position of the enone increased the propensity for 1,2-addition.

(6) The use of HMPA had minimal effect on the regioselectivity.

The interesting properties of various cerium reagents prompted us to investigate the reactions of cerium amide enolates with aldehydes, ketones and α,β-unsaturated enones. The first part of this thesis describes the results of this investigation.

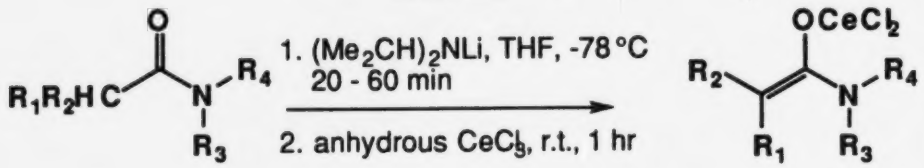
Results and Discussion

The generation of the cerium amide enolates was very straightforward. It simply involved the transmetallation of the corresponding lithium enolate with a suspension of anhydrous cerium(III) chloride in dry THF at -78 °C for at least one hour. Anhydrous cerium(III) chloride was prepared by heating $CeCl_3 \bullet 7H_2O$ at 100 °C at 1 torr for two hours in a Kugelrohr distillation apparatus and another two hours at 150 °C. The lithium enolate was obtained by deprotonation of the corresponding amide with LDA at -78 °C. Evans and co-workers discovered that deprotonation of amide **4** with LDA gave a single detectable enolate isomer, assigned the *Z*-configuration on the basis of mechanistic considerations and the stereochemical outcome of subsequent reactions.[19 20] By analogy, *N,N*-dimethylpropionamide **2** is likely to give the *Z*-enolate too. It is reasonable to assume that the geometry of the lithium enolates was not changed during the transmetallation process (Scheme 1-1). The transmetallation processes were accompanied by a color change of the suspension from yellowish brown ($CeCl_3$ only) to pink (**5**) and purple (**7**), an indication of the changes in ligands or complexation states for the cerium(III) ion.

The addition of the cerium enolate to an aldehyde or a ketone was usually carried out at -78 °C and monitored with thin-layer chromatography. After completion, the reaction mixture was quenched with a saturated aqueous solution of KH_2PO_4. The resulting mixture was extracted with an organic solvent. We discovered that dichloromethane was a better solvent than ether, since the loss of the β-hydroxyamide to the aqueous layer was minimal using the former solvent, especially with smaller molecules. Pure products were obtained by column chromatography.

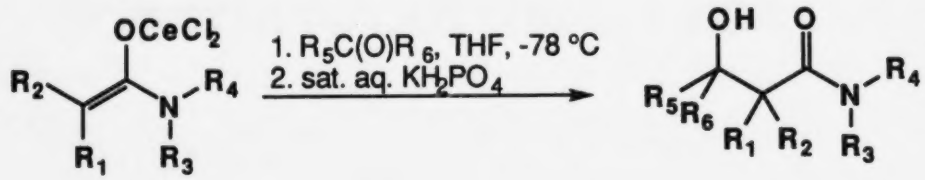
The ratio between the cerium amide enolate and the carbonyl compound was usually 2.4 - 2.1 : 1. Our results showed that it was necessary to use at least 2 moles of the reagent for 1 mole of the carbonyl compound. When only 1 mole of the dichlorocerioacetamide derivative **5** were used to react with 1 mole of cyclohexanone, only 43% of the desired adduct was isolated, while the yield was around 90% when 2.1 moles of **5** was used for 1 mole of cyclohexanone. This result was in agreement with the general observations for the nucleophilic addition of cerium(III) reagents.[13,15,17] Due to the lack of understanding of the nature of this type of reagents, their aggregation states and the reaction mechanism, this observation could not be clearly explained.

Scheme 1-1



1. $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$
2. $R_1 = H$, $R_2 = CH_3$, $R_3 = R_4 = CH_3$
3. $R_1 = R_2 = CH_3$, $R_3 = R_4 = CH_3$
4. $R_1 = H$, $R_2 = CH_3$, $R_3, R_4 = -(CH_2)_4-$

5. $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$
6. $R_1 = H$, $R_2 = CH_3$, $R_3 = R_4 = CH_3$
7. $R_1 = R_2 = CH_3$, $R_3 = R_4 = CH_3$
8. $R_1 = H$, $R_2 = CH_3$, $R_3, R_4 = -(CH_2)_4-$

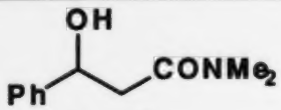
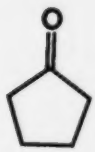
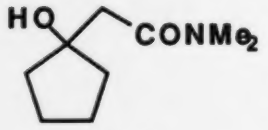
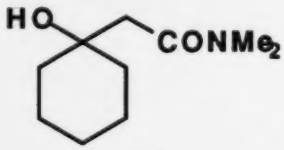
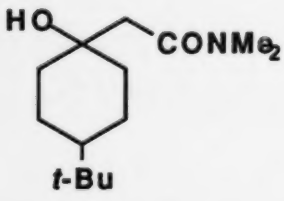
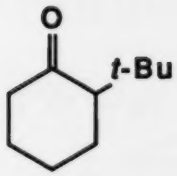
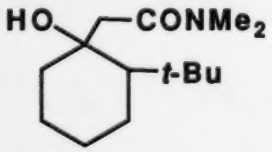
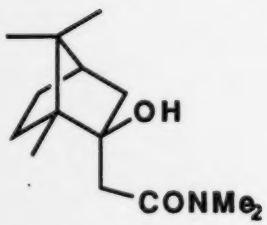


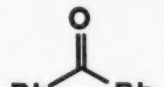
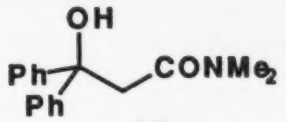
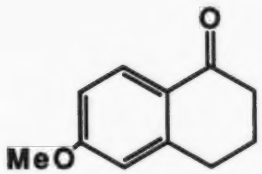
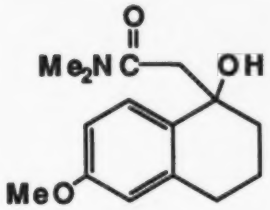
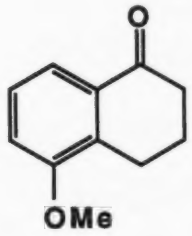
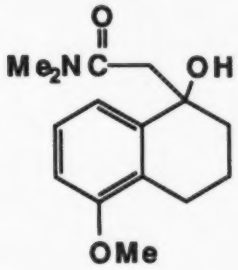
The addition reactions of the cerium enolate of *N,N*-dimethylacetamide (**5**) were investigated first and the results are summarized in Table 1-8. For comparison, the yields for the addition reactions of the lithium enolate to a few

selected aldehyde and ketones are also listed in Table 1-8. These yields were either taken from the report of Hullot *et al.*[21] or obtained from our own experiments under the same reaction conditions. The structure characterization was achieved by spectroscopic methods. The hydroxy group usually gave a broad band at 3400 - 3250 cm^{-1} in the IR spectrum. The carbonyl stretching vibration for the amide group appeared at 1630 - 1610 cm^{-1} as a strong and sharp band. In the ^1H NMR spectrum, the hydroxy proton usually gave a broad peak at 7 - 4 ppm. The two methyl groups on the amide nitrogen resonated at 3.1 - 2.6 ppm, while the two α-protons of the amide group appeared at 3.2 - 2.2 ppm. High resolution mass spectrometry usually could register the molecular ion peak. Elemental analysis of some products further confirm the structural assignments. When more than one stereoisomer was possible, we concentrated our effort more on the yields rather than on the stereoselectivity and the stereochemical assignments of the product (Entries 4 and 5).

Generally speaking, the yields were excellent due to the unhindered nature of this cerium enolate. Only in one case did we observe a moderate yield (Entry 8), which was caused by the low electrophilicity of the ketone due to the presence of a methoxy group *para* to the carbonyl group. With benzaldehyde (Entry 1), the yield was much higher for the cerium enolate than for the lithium one. With 4-*tert*-butylcyclohexanone, two isomers were obtained in a ratio of 53 to 47, indicating a lack of selectivity between the axial and equatorial attacks. However, with 2-*tert*-butylcyclohexanone and (+)-camphor, only one isomer was produced in each case (Entries 5 and 6). The stereochemistry of compound **5** was not determined. The addition to (+)-camphor provided the *endo*-adduct **6**, as proved by nuclear Overhauser effect (NOE) experiments (Figure 1-1). With this hindered ketone, the cerium enolate offered a somewhat better yield than the lithium one.

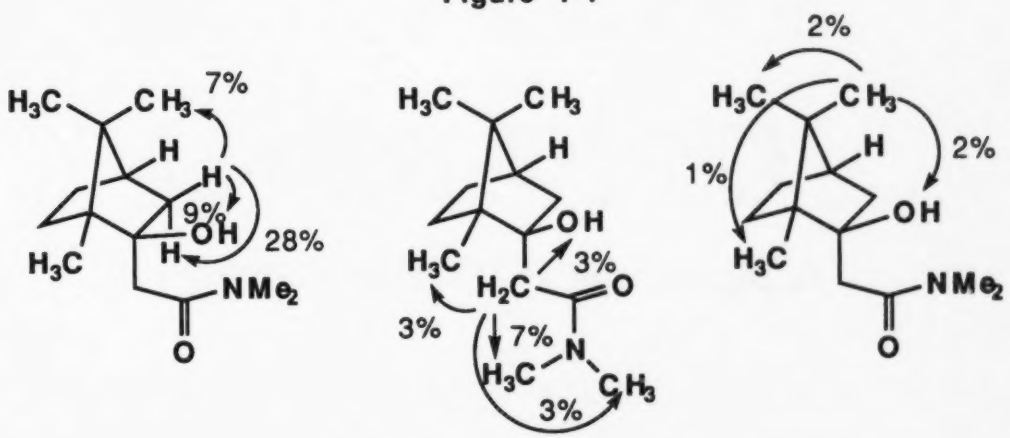
Table 1-8: The addition of the cerium enolate of *N,N*-dimethylacetamide (**5**) to aldehydes and ketones

Entry	Substrate	Product	Time & Temperature	Yield (%) Ce / Li
1	PhCHO	 **9**	1 hr, -78 °C	99 / 68[a]
2		 **10**	30 min, -78 °C	86 /
3		 **11**	20 min, -78 °C	89 / 86[a]
4		 **12a, 12b**	1 hr, -78 °C	99 /
5		 **13**	3.5 hr, -78 °C	96 /
6		 **14**	3 hr, -78 °C	98 / 93

7		 **15**	1 hr, -78 °C	92 / 93[a]
8		 **16**	25 hr, -60 °C	65 /
9		 **17**	35 min, -78 °C	89 /

[a]Yield for the lithium enolate was taken from reference 21.

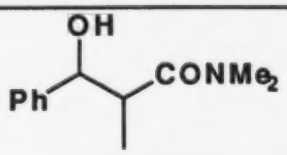
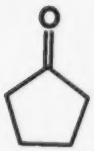
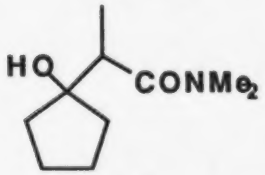
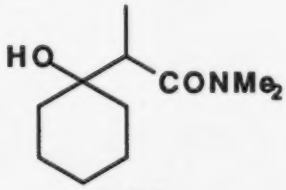
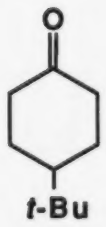
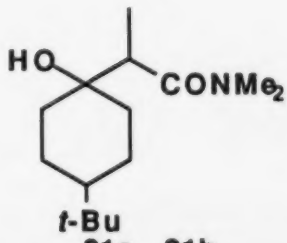
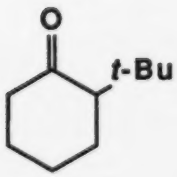
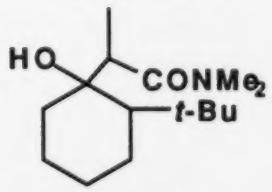
Figure 1-1

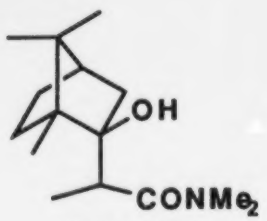
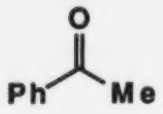
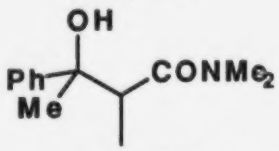
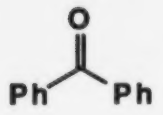
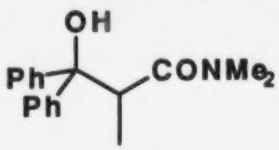
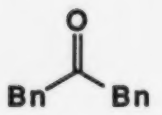
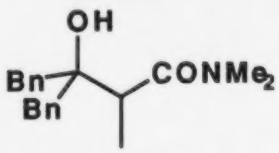
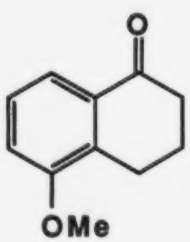
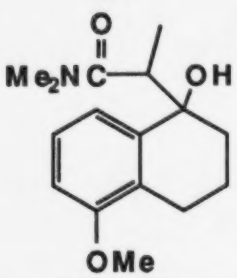


Encouraged by these promising results, we proceeded to investigate the effect of substitution at the α-carbon of the amide. *N,N*-Dimethylpropionamide **2** was chosen as an example of the monosubstituted ones. Its cerium enolate **6**

was prepared and reacted with a number of selected aldehyde and ketones. The results are listed in Table 1-9. The structure characterization was done by spectroscopic methods. The hydroxy group usually gave a broad band at 3400 - 3250 cm^{-1} in the IR spectrum. The carbonyl stretching vibration for the amide group appeared at 1630 - 1610 cm^{-1} as a strong and sharp band. In a typical ^1H NMR spectrum, the two methyl groups on the amide nitrogen resonated at 3.2 - 2.6 ppm, while the α-proton of the amide group appeared at 3.8 - 2.5 ppm as a quartet or a doublet of quartets. The α-methyl group of the amide appeared as a doublet at 1.3 - 0.8 ppm. High resolution mass spectrometry usually could register the molecular ion peak. Elemental analysis of some products further confirm the formula. Because of the introduction of a stereogenic center at the α-carbon of the amide, diastereomers were produced with aldehydes and unsymmetric ketones. The ratios of these diastereomers, which were determined by the integrals in the ^1H NMR spectra, are also listed in Table 1-9. No effort was made to assign the relative stereochemistry of these diastereomers. Again, excellent yields were obtained. In certain cases where the yields were low with the lithium enolate, improved yields were observed with the cerium one **6** (Entries 6, 8 and 9). With (+)-camphor and benzophenone, the high yields were an indication of the ability of the cerium enolate to react with hindered ketones. With the highly enolizable 1,3-diphenyl-2-propanone, the high yield obtained from the cerium enolate could be attributed to the low basicity of the reagent. Compared with the low selectivity of **5** with 4-*tert*-butylcyclohexanone between the axial and equatorial attacks, enolate **6** demonstrated a much better differentiation between them.

Table 1-9: The addition of the cerium enolate of *N,N*-dimethylpropionamide (**7**) to aldehyde and ketones

Entry	Substrate	Product	Time & Temperature	Ratio of diaste-reomers[a]	Yield (%) Ce / Li
1	PhCHO	 **18a, 18b**	20 min, -78 °C	53 / 47	90 /
2		 **19**	90 min, -78 °C		85 /
3		 **20**	40 min, -78 °C		94 /
4		 **21a, 21b**	40 min, -78 °C	71 / 29	98 /
5		 **22a, 22b**	5 hr, -78 °C	72 / 28	97 /

6		 **23a, 23b**	8 hr -78 °C	95 / 5	94 / 57
7		 **24a, 24b**	2 hr -78 °C	62 / 38	86 /
8		 **25**	40 min, -78 °C		97 / 86[b]
9		 **26**	40 min, -78 °C		92 / 82
10		 **27a, 27b**	40 min, -78 °C	85/ 15	98 /

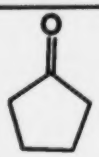
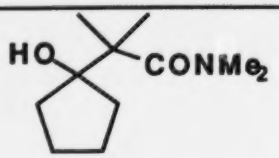
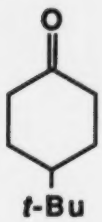
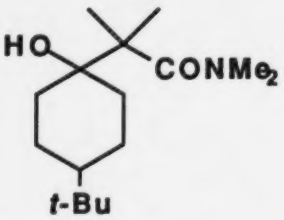
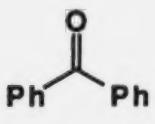
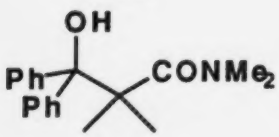
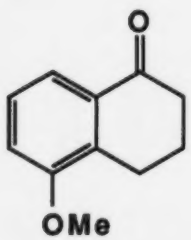
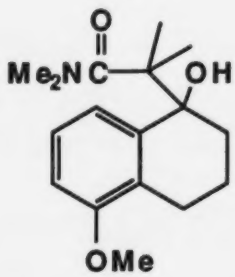
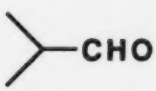
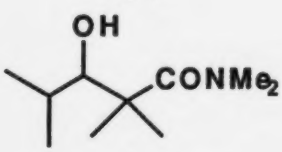
[a]Ratio of diastereomers in the isolated products mixture when the cerium enolate **6** was used.

[b]Yield for the lithioisovaleramide enolate derivative was taken from reference 21.

Having studied the monosubstituted amide, we decided to examine the reactivity of disubstituted amide enolate. Enolate **7** was prepared from *N,N*-

dimethylisobutyramide. A number of selected ketones were reacted with this enolate (Table 1-10). Surprisingly, no addition product was ever isolated at low temperature (-78 °C to -60 °C, Entries 1, 3 and 4). With 4-*tert*-butyl-cyclohexanone, a series of experiment was done to establish the temperature profile of the addition reaction. The temperature was allowed to increase in a stepwise manner from -43 °C to room temperature and aliquots of the reaction mixture were taken at different temperatures, worked up and subjected to GC-MS analysis. No desired product was observed. With isobutyraldehyde, 51% of product **32** was isolated with the cerium enolate **7** and 47% with the lithium enolate after 20 hr at -78 °C. This low reactivity was probably attributable to the high steric demand of the reagent. It differed sharply from the ester enolates. The cerium enolate of ethyl isobutyrate reacted smoothly with cyclopentanone and 5-methoxy-α-tetralone, providing the adduct in 97% yield in each case (Table 1-5).[14] The behaviour of the cerium amide enolate **7** was similar to that of the cerium enolate of isobutyronitrile, which failed to react with diethyl ketone even in refluxing THF.[16,17]

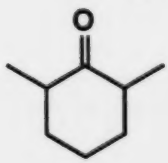
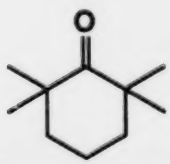
Table 1-10: The addition of the cerium enolate of *N,N*-dimethylisobutyramide amide (**7**) to aldehyde and ketones

Entry	Substrate	Product	Time & Temperature	Yield (%) Ce / Li
1		 **28**	3 d, -78 °C or 1 d, -60 °C	0 / 0 /
2		 **29**	-43 °C to room temperature	0 /
3		 **30**	20 hr, -78 °C	0 / 0[a]
4		 **31**	23 hr, -78 °C	0 /
5		 **32**	20 hr, -78 °C	51 / 47

[a] Yield taken from reference 21.

Next, we set out to compare the reactivities of the cerium and lithium enolates with hindered ketones. As discussed previously, the cerium enolates **5** and **6** offered higher yields with camphor than the lithium enolates (also listed in Table 1-11, Entries 1 and 2). With 2,6-dimethylcyclohexanone, both the cerium and lithium enolates of *N,N*-dimethylpropionamide gave comparable yields of adduct . Neither of them gave any product when reacted with 2,2,6,6-tetramethylcyclohexanone at -15 °C for 20 hr and then 5 °C for 60 hr.

Table 1-11: Comparison of the addition reaction of lithium and cerium amide enolates to hindered ketones.

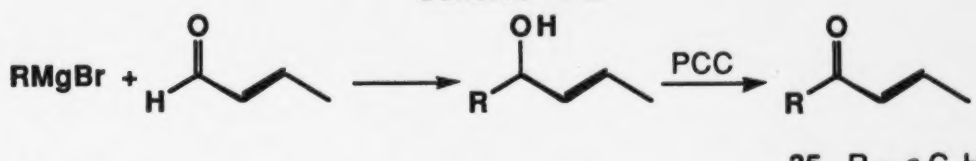
Entry	Amide	Ketone	Cerium enolate	Lithium enolate
1	$MeCONMe_2$		3 hr, -78 °C, 98%	48 hr, -78 °C, 93%
2	$EtCONMe_2$		20 hr, -78 °C, 94%	48 hr, -78 °C, 57%
3	$EtCONMe_2$		1 hr, -78 °C, 88%	5 hr, -78 °C, 89%
4	$EtCONMe_2$		20 hr, -15 °C and 60 hr at 5 °C, 0%	20 hr, -15 °C and 60 hr at 5 °C, 0%

With highly enolizable ketones, the cerium enolates of esters and nitriles demonstrated lower basicity towards the substrates than the corresponding lithium enolates. Less enolization of the substrates translated into higher yields for the desired adducts. The same trend was observed here with the cerium amide enolates. As we have seen in Table 1-9 (Entry 9), a higher yield (92%) was obtained with the cerium enolate **6** with 1,3-diphenyl-2-propanone than with its lithium analog (82%). However, when the enolates of *N,N*-dimethylacetamide were reacted with 5-methoxy-β-tetralone, comparable yields (around 65%) were obtained using either the cerium or the lithium enolate.

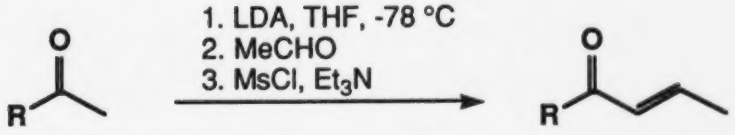
Having systematically studied the addition to saturated aldehydes and ketones, we then set out to investigate the regioselectivity of the cerium amide enolates towards conjugated α,β-enones. In order to compare with the results reported by Heathcock and co-workers, the same enones (**35** - **39**) were used.[18] They were prepared either by the nucleophilic addition of a Grignard reagent to crotonaldehyde followed by oxidation of the resulting alcohol to the ketone, or by an aldol addition of a ketone enolate to acetaldehyde followed by dehydration, as described by Heathcock *et al.* (Scheme 1-2). The lithium enolate of *N,N*-dimethylacetamide gave predominately the 1,2-adducts, while the lithium enolate of *N,N*-dimethylisobutyramide gave mainly the 1,4-adducts. The enolate of propionamide was a switch point, where both the 1,2- and 1,4-adducts were obtained in most cases. We decided to use **4**, *N*-propionylpyrrolidine for our study. Its cerium enolate **8** was prepared and reacted with the enones. The results are summarized in Table 1-12 and compared with those reported by Heathcock and co-workers. Due to the presence of two stereogenic centers in the 1,2- and 1,4-adducts, two diastereomers each were produced for the 1,2- and 1,4-adducts. The separation of the 1,2-adducts from the 1,4-adducts was usually easy by

chromatography. Sometimes the two 1,2-adducts could also be separated from each other. But the separation of the two 1,4-adducts were never achieved due to the closeness of their R_f values. The structural assignments of the these adducts were achieved by spectropic analysis. The spectral data were compared and were in agreement with those reported by Heathcock and co-workers. Since it was not our main focus to observe the stereoselectivity, the ratios of these diastereomers are not discussed here. Instead, they are described in the Experimental section.

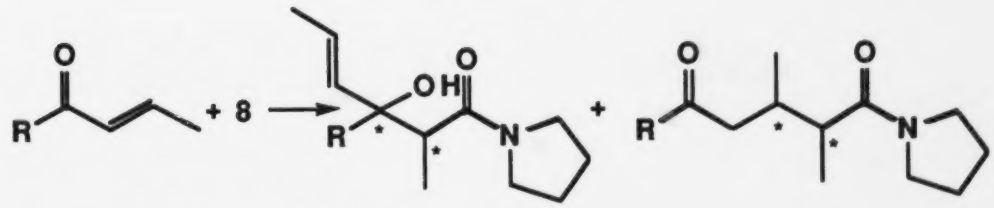
Scheme 1-2



35 R = *c*-C_6H_{11}
36 R = *t*-Bu



37 R = *i*-Pr
38 R = Ph
39 R = *p*-BrC_6H_4



In almost all the cases examined, the ratios of the 1,2-adducts to the 1,4-adducts were increased, despite the lack of exclusive formation of the 1,2-adducts. With (*E*)-1-phenyl-2-buten-1-one (**38**), the ratio of the 1,2- / 1,4-

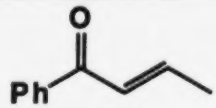
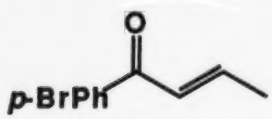
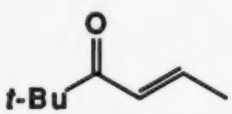
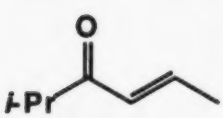
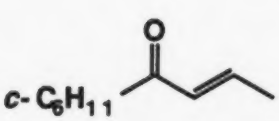
adducts was increased to 69 / 31 using the cerium enolate from 12 / 88 observed for the lithium enolate (Entry 1). With (*E*)-1-(*p*-bromophenyl)-2-buten-1-one (**39**), the ratio was increased slightly from 50 / 50 to 65 / 35 (Entry 2). Carrying out the transmetallation at room temperature did not seem to enhance the ratio for the 1,2-adducts. On the other hand, prolonged treatment at even -78 °C seemed to shift the kinetically favored 1,2-adducts to the thermodynamically more stable 1,4-adducts (Entries 2 and 3). With (*E*)-2,2-dimethyl-4-hepten-3-one (**36**), due to the large *t*-butyl group on the carbonyl, no 1,2-adduct was found with either the cerium or the lithium enolate (Entry 4). With (*E*)-2-methyl-4-hepten-3-one (**37**), the increase in the preference for 1,2-addition was also very profound, from 29 / 71 for the lithium enolate to 80 / 20 for the cerium enolate (Entry 5).

The behavior of cerium amide enolate **8** contradicted those of all the other cerium enolates derived from ketones, esters and nitriles in the formation of large amount of 1,4-adducts, despite the enhancement in the 1,2- / 1,4-adduct ratio. A reasonable rationale for this, as it seemed to us at that point, was that there existed an equilibrium between the cerium enolate and the lithium enolate. The lithium enolate was responsible for the formation of the 1,4-adducts. The ratio of these two enolates could not be directly derived from the 1,2- / 1,4-adduct ratio, since the two enolates might react at different rates. Addition of chelating agents specific for the lithium ion was expected to shift the equilibrium towards the cerium enolate side, thus increasing the 1,2- / 1,4-adduct ratio. Addition of 5 equivalents of hexamethylphosphoramide (HMPA) failed to register the desired effect. On the contrary, a decrease in the 1,2- / 1,4-ratio was observed (Entry 6). Similarly, with (*E*)-1-cyclohexyl-2-buten-1-one (**37**), the ratio of 1,2- / 1,4-addition was increased from 40 / 60 to 80 / 20 by using the cerium enolate in place of the lithium enolate. Addition of HMPA to

the cerium enolate suspension before the addition of the enone decreased the selectivity for the 1,2-addition. 12-Crown-4 is capable of selectively chelating lithium ion in the presence of other ions like cerium (III). Addition of this crown ether to the cerium enolate suspension before the addition of the enone also decreased the selectivity for the 1,2-addition (Entries 9 and 10). This trend was opposite to what we expected to see. Due to the lack of a thorough understanding of these cerium reagents, this observation can not be explained.

In conclusion, an efficient procedure for the generation of cerium enolates of *N,N*-dialkylated amides and the application of these enolates to the addition reactions to aldehydes, ketones and conjugated enones were systematically investigated. With certain saturated aldehydes and ketones, higher yields were obtained with the cerium enolates than the lithium ones. In general, the cerium enolates reacted better with sterically hindered or highly enolizable ketones. With conjugated enones, improvement in various degrees in the selectivity of 1,2-addition over 1,4-addition was observed.

Table 1-12: Addition of the cerium and lithium enolates of *N*-propionylpyrrolidine to enones

Entry	Enone	Cerium		Lithium[a]	
		Temp., Time and Yield	1,2 / 1,4	Temp., Time and Yield	1,2 / 1,4
1	 **38**	4 hr, -78 °C, 30%	69 : 31	1 hr, -78 °C, 92%	12 : 88
2	 **39**	0.6 hr, -78 °C, 90%	65 : 35	1 hr, -78 °C, 84%	50 : 50
3	**39**	10 hr, -78 °C, 100%	52 : 48		
4	 **36**	1.6 hr, -78 °C, 81%	<3 : 97[b]	1 hr, -78 °C, 90%	<3 : 97
5	 **37**	1 hr, -78 °C, 33%	80 : 20	0.8 hr, -78 °C, 84%	29 : 71
6	**37**	3.5 hr, -78 °C, 34%	55 : 45[c]		
7	 **34**	7 hr, -78 °C, 76%	80 : 20	1 hr, -78 °C, 56%	40 : 60

8	**34**	4.5 hr, -78 °C, 94%	28 : 72[d]
9	**34**	8 hr, -78 °C, 68%	71 : 29[e]
10	**34**	20 hr, -78 °C, 73%	43 : 57[f]

[a]Taken from reference 21.

[b]No 1,2-adducts were observed in the ^{1}H NMR spectrum of the crude product.

[c]Before transmetallation, HMPA (HMPA : $CeCl_3$: LDA = 5.4 : 1.0 : 1.0) was added to the lithium enolate solution and it was stirred at room temperature for 30 min.

[d]Before transmetallation, HMPA (HMPA : $CeCl_3$: LDA = 5.2 : 1.0 : 1.0) was added to the lithium enolate solution and it was stirred at room temperature for 1 hr.

[e]Before transmetallation, 12-crown-4 (crown ether : LDA = 1.0 : 1.0) was added to the lithium enolate solution and it was stirred at room temperature for 60 min.

[f]Before transmetallation, 12-crown-4 (crown ether : LDA = 1.3 : 1.0) was added to the lithium enolate solution and it was stirred at room temperature for 30 min.

Experimental

General

Melting points were recorded on a Koefler hot stage apparatus and are uncorrected. Infrared spectra (IR) were recorded using Nicolet 7-199, Nicolet MX-1 or Perkin-Elmer FTIR spectrometers. High resolution mass spectra (HRMS) were recorded using a Kratos AEI MS-50 high resolution mass spectrometer. Low resolution mass spectra (MS) were obtained using an AEI MS-12 mass spectrometer. Chemical ionization mass spectra (CIMS) were obtained using an AEI MS-12 mass spectrometer with ammonia as the reagent gas. Elemental analyses were carried out by the microanalytical laboratory of this department. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using the following spectrometers: Bruker AM-200 (200 MHz), Bruker AM-300 (300 MHz), Bruker AMR-300 (300 MHz), Bruker AMR-360 (360 MHz), Bruker AM-400 (400 MHz) and Varian Unity 500 (500 MHz). Coupling constants are reported to within ±0.5 Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded using the following spectrometers: Bruker AM-200 (50 MHz), Bruker AM-300 (75 MHz), Bruker WH-400 (100 MHz) and Varian Unity 500 (125 MHz). Carbon-13 multiplicities were derived from Carr-Purcel-Meiboom-Gill spin echo J-modulated experiments (attached proton test, or APT). Methylene groups and quaternary carbons appeared as in-phase (p) with respect to the deuteriochloroform signal while the signals anti-phase (ap) to that of deuteriochloroform were due to the methyl and methine groups. Nuclear

Overhauser enhancement (NOE) experiments were carried out in the difference mode in which a blank (unirradiated) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals being antiphase with respect to the irradiated signal.

Reactions requiring anhydrous conditions were performed in flame-dried glassware, assembled and allowed to cool while being purged with a stream of argon. Reactions were carried out under argon and monitored by analytical thin-layer chromatography (t.l.c.) performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. The visualization of the chromatograms was done by looking under an ultraviolet lamp (λ = 254 nm) and / or dipping in an ethanol solution of phosphomolybdic acid (5%, w/v) followed by hot plate charring. Products were purified by flash chromatography using silica gel 60 (230 - 400 mesh), unless otherwise indicated. Solvents were removed under reduced pressure on a rotary evaporator.

Materials

All the amides were dried with molecular sieve (4Å) and fractionally distilled. The saturated aldehydes and ketones were commercially available. The α,β-unsaturated enones were prepared according to reported procedures.[18]

Skelly B refers to Skelly Oil Company light petroleum, bp 62 - 70 °C. Skelly B was distilled prior to use. Solvents and liquid reagents used in this and the following chapters were dried and distilled under an argon atmosphere prior to use as follows: tetrahydrofuran (THF), ether, benzene and dimethoxyethane (DME) from a blue-purple solution of sodium benzophenone

ketyl; dichloromethane, diisopropylamine, *N,N,N',N'*-tetramethylethylenediamine, pyridine, triethylamine and hexamethylphosphoramide (HMPA) from calcium hydride; chloroform from potassium carbonate; *N,N*-dimethylformamide from barium oxide under reduced pressure; ethanol from magnesium. Argon was passed through a column of 4 Å molecular sieves and self-indicating silica gel. Anhydrous magnesium sulfate was used for drying organic solutions.

General procedures for the preparation of cerium amide enolates and subsequent reactions with carbonyl compounds:

(1) Anhydrous cerium(III) chloride:

Cerium(III) chloride heptahydrate ($CeCl_3 \bullet 7H_2O$) (1.36 g, 3.64 mmol) was ground to a powder in a 50 mL round-bottomed flask with a magnetic stirring bar. The flask was heated at 100 °C under vacuum (about 1 torr) in a Kugelrohr distillation apparatus for 2 hr. The temperature was then gradually increased to 150 °C and the heating was continued for another 2 hr. After the dried cerium chloride was cooled to room temperature under vacuum, a pre-weighed rubber septum was put on the flask and the amount of the dried cerium chloride determined. Freshly distilled THF (10 mL) was added and the resulting suspension was stirred vigorously under argon at room temperature for at least 1 hr before the transmetallation process with the lithium amide enolate.

(2) Preparation of a lithium amide enolate:

To a stirred solution of diisopropylamine (405 mg, 4.0 mmol) in dry THF (5 mL) was added *n*-BuLi (3.7 M, 1.1 mL, 4.0 mmol) dropwise at -78 °C. The resulting solution was stirred at the same temperature for 20 min under argon. An amide (3.7 mmol) in THF (2 mL) was added to the lithium diisopropylamide (LDA) solution at -78 °C and the mixture was stirred for another 25 min at the same temperature.

(3) Transmetallation of the lithium amide enolate with $CeCl_3$ to generate the cerium amide enolate:

The cerium chloride suspension in THF was cooled to -78 °C with a dry ice-acetone bath. To this suspension was quickly added the lithium amide enolate solution via a canula, with an argon inlet attached to the flask containing the enolate solution and an argon outlet attached to the flask containing the cerium chloride suspension. The mixture was vigorously stirred at -78 °C under argon for at least 1 hr. This process was accompanied by a color change from the usually pale yellow color of the cerium chloride suspension to a light pink color for **5** and a purple color for **7**.

(4) Addition of a cerium amide enolate to a carbonyl compound:

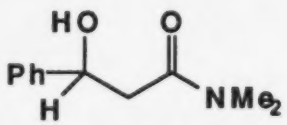
The carbonyl compound (2.0 mmol) dissolved in a small amount of THF was added dropwise to the cerium enolate (4.0 - 5.0 mmol) via a canula at -78 °C and the reaction mixture was stirred at the same temperature unless otherwise indicated and monitored by thin-layer chromatography. After the completion of the reaction, the reaction mixture was quenched with saturated aqueous KH_2PO_4 solution at -78 °C and extracted with dichloromethane

(3 x 20 mL). The combined extracts were washed with water and saturated sodium chloride solution, dried with $MgSO_4$, filtered and concentrated. The residue was subjected to flash column chromatography (eluting with methanol in dichloromethane) to afford the adduct(s). The reaction time, temperature and yield(s) are given in the Results and Discussion section. The ratio of two isomers, where applicable, was determined by the intergrals in the ^1H NMR spectrum.

General procedures for the addition of a lithium amide enolate to a carbonyl compound:

The steps (2) and (4) of the above described procedure were applied similarly, using a lithium amide enolate. The volume of the lithium enolate solution was about 15 mL so that the overall volume of the reaction mixture was comparable to those with the cerium enolates.

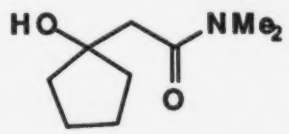
3-Hydroxy-*N,N*-dimethyl-3-phenylpropionamide (9)



Compound **9** (colorless oil): IR (CCl_4, cast): 3395 (br, st, OH), 1627 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H, phenyl), 5.15 (dd, J_1 = 9.3 Hz, J_2 = 3.1 Hz, 1H, HOC**H**CH_2), 4.15 (br s, 1H, **H**O$CHCH_2$), 2.99 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 2.73 (dd, J_1 = 16.5 Hz, J_2 = 3.1 Hz, 1H, HOCHC**H**$_2$), 2.63 (dd, J_1 = 16.5 Hz, J_2 = 9.3 Hz, 1H, HOCHC**H**$_2$); ^{13}C NMR APT

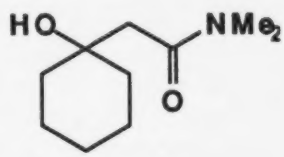
(75 MHz, $CDCl_3$): δ 172.30 (p), 143.08 (p), 128.46 (ap), 127.50 (ap), 125.76 (ap), 70.40 (p), 41.93 (p), 37.08 (ap), 35.26 (ap); MS M^+: 193.

1-(*N,N*-Dimethylcarbamoylmethyl)cyclopentanol (10)



Compound **10** (colorless oil): IR (CH_2Cl_2, cast): 3400 (br, st, -OH), 1628 cm^{-1} (st, C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 4.77 (br s, 1H, OH), 3.03 (s, 3H, *N*-CH_3), 2.97 (s, 3H, *N*-CH_3), 2.56 (s, 2H, CH_2C=O), 1.85 (m, 4H), 1.59 (m, 2H), 1.48 (m, 2H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 172.97 (p), 79.69 (p), 41.98 (p), 39.88 (p), 37.16 (ap), 35.03 (ap), 23.75 (p); HRMS M^+: 171.1261 (calcd. for $C_9H_{17}NO_2$: 171.1259).

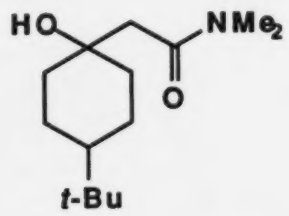
1-(*N,N*-Dimethylcarbamoylmethyl)cyclohexanol (11)



Compound **11** (white, low melting solid): IR (CCl_4, cast): 3393 (br, md, OH), 1625 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.22 (br s, 1H, OH), 3.02 (s, 3H, *N*-CH_3), 2.98 (s, 3H, *N*-CH_3), 2.40 (s, 2H, CH_2C=O), 1.8 - 1.2 (m, 10H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 172.97 (p), 70.11 (p), 42.13 (p), 37.89 (p), 37.48 (ap), 35.21 (ap), 25.92 (p), 22.06 (p); MS M^+: 185. Anal. calcd. for

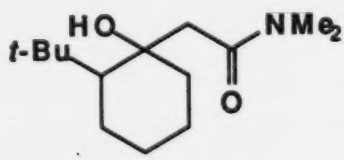
$C_{10}H_{19}NO_2$: C 64.83%, H 10.34%, N 7.56%; found: C 64.63%, H 10.48%, N 7.49%.

4-*tert*-Butyl-1-(*N,N*-dimethylcarbamoylmethyl)cyclohexanols (12a and 12b)



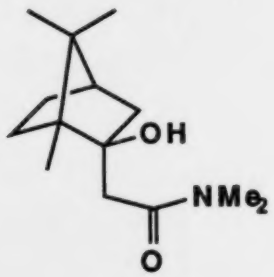
A mixture of **12a** and **12b** (53 : 47, white crystals): IR (CCl_4, cast): 3403 (md, OH), 1620 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 and 8.90 (br s, 1H each, O**H**), 3.06, 3.01, 2.98 and 2.96 (s, 3H each, *N*CH_3), 2.53 (major) and 2.38 (minor) (s, 2H each, CH_2C=O), 1.9 - 0.9 (m, 16H), 0.86 (s, 18H, *t*-Butyl); ^{13}C NMR APT ($CDCl_3$, 75 MHz): 172.98 (p), 70.93 (p), 69.37 (p), 48.16 (ap), 47.40 (ap), 43.64 (p), 38.43 (p), 38.19 (p), 37.45 (ap), 36.89 (p), 35.29 (ap), 35.15 (ap), 32.46 (p), 32.24 (p), 27.65 (ap), 27.59 (ap), 24.52 (p), 22.28 (p); MS M^+: 241. Anal. calcd. for $C_{14}H_{27}O_2N$: C 69.67%, H 11.27%, N 5.80%; found: C 69.67%, H 11.15%, N 5.70%.

2-*tert*-Butyl-1-(*N,N*-dimethylcarbamoylmethyl)cyclohexanol (13)



Compound **13** (white crystals, only one isomer observed): IR (CCl_4, cast): 3373 (br, st, OH), 1622 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (br s, 1H, O**H**), 3.07 (s, 3H, NC**H**$_3$), 2.97 (s, 3H, NC**H**$_3$), 2.91 (d, J = 14.6 Hz, 1H, C**H**$_2$C=O), 2.56 (d, J = 14.6 Hz, 1H, C**H**$_2$C=O), 1.68 (m, 5H), 1.38 (m, 1H), 1.20 (m, 3H), 1.06 (s, 9H, *t*-Butyl); ^{13}C NMR APT (50 MHz, $CDCl_3$): 173.96 (p), 74.90 (p), 54.16 (ap), 42.78 (p), 39.36 (p), 37.82 (ap), 35.25 (ap), 31.43 (ap), 26.43 (p), 24.37 (p), 21.76 (p); MS M^+: 241. Anal. cacld. for $C_{14}H_{27}NO_2$: C 69.67%, H 11.27%, N 5.80%; found: C 69.69%, H 10.88%, N 5.85%.

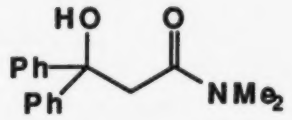
(1R,2S,4R)-2-(*N,N*-Dimethylcarbamoylmethyl)borneol (14)



Compound **14** (white crystals, ethanol - hexanes): mp 95.5 - 97.5 °C; IR (KBr): 3267 (br, st, OH), 1618 cm^{-1} (st, C=O); MS M^+: 239; ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (br s, 1H, O**H**), 3.05 (s, 3H, *N*-C**H**$_3$), 2.98 (s, 3H, *N*-C**H**$_3$), 2.55 (d, J = 16.0 Hz, 1H, C**H**$_2$C=O), 2.41 (d, J = 16.0 Hz, 1H, C**H**$_2$C=O), 2.20 (pseudo dt, J_1 = 13.5 Hz, $J_2 = J_3$ = 3.8 Hz, 1H, C**H**$_2$COH), 1.72 (m, 1H), 1.35 (m, 3H), 1.17 (s, 3H, CH_3), 0.96 (m, 1H), 0.88 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 178.45 (p), 79.78 (p), 52.26 (p), 50.27 (p), 49.06 (p), 44.80 (ap), 41.84 (ap), 37.59 (ap), 35.55 (ap), 30.08 (p), 27.78 (p), 21.51 (ap), 20.95 (ap), 13.13 (ap), 12.46 (ap); HRMS M^+: 239.1889 (calcd. for $C_{14}H_{25}NO_2$:

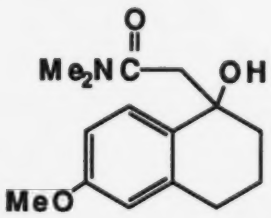
239.1885). Anal. calcd. for $C_{14}H_{25}NO_2$: C 70.25%, H 10.53%, N 5.85%; found: C 69.93%, H 10.20%, N 5.73%.

3-Hydroxy-*N,N*-dimethyl-3,3-diphenylpropionamide (15)



Compound **15** (white crystals, ethanol and hexanes): mp 104.5 - 105.0 °C; IR (CCl_4, cast): 3300 (br, w, OH), 1624 cm^{-1} (st, C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 4H, phenyl), 7.30 (m, 4H, phenyl), 7.21 (m, 2H, phenyl), 6.68 (br s, 1H, OH), 3.21 (s, 2H, CH_2C=O), 3.02 (s, 3H, *N*-CH_3), 2.68 (s, 3H, *N*-CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 172.25 (p), 146.87 (p), 128.15 (ap), 126.85 (ap), 125.82 (ap), 76.73 (p), 42.44 (p), 37.27 (ap), 35.28 (ap); HRMS: M^+ 269.1415 (calcd. for $C_{17}H_{20}NO_2$: 269.1415). Anal. calcd. for $C_{17}H_{20}NO_2$: C 75.81%, H 7.11%, N 5.2%; found: C 75.68%, H 7.11%, N 5.03%.

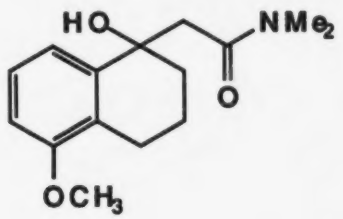
1-(Dimethylcarbamoylmethyl)-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (16)



Compound **16**: IR (CH_2Cl_2, cast): 3359 (br, md, OH), 1616 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 8.6 Hz, 1H, aromatic), 6.78 (dd,.

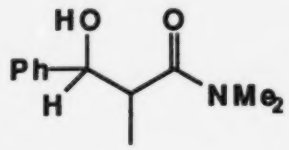
J_1 = 8.6 Hz, J_2 = 2.9 Hz, 1H, aromatic), 6.58 (d, J = 2.9 Hz, 1H, aromatic), 3.79 (s, 3H, OCH_3), 2.98 (s, 3H, NCH_3), 2.91 (s, 3H, NCH_3), 2.90 - 2.65 (m, 4H, $CH_2C{=}O$ and $ArCH_2CH_2CH_2$), 2.05 (m, 3H, $ArCH_2CH_2CH_2$ and $ArCH_2CH_2CH_2$), 1.71 (m, 1H, $ArCH_2CH_2CH_2$); HRMS M^+: 263.1531 (calcd. for $C_{15}H_{21}NO_3$: 263.1521).

1-(Dimethylcarbamoylmethyl)-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (17)



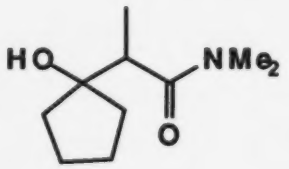
Compound **17** (white crystals, EtOH - hexane): mp 117.5 - 118.5 °C; IR (KBr): 3308 (st, OH), 1610 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, aromatic proton), 7.19 (pseudo t, J = 7.8 Hz, 1H, aromatic proton), 6.73 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, aromatic proton), 6.04 (s, OH), 3.82 (s, 3H, OCH_3), 2.98 (s, 3H, *N*-CH_3), 2.90 (s, 3H, *N*-CH_3), 2.79 (d, J = 15.5 Hz, 1H, $CH_2C{=}O$), 2.70 (d, J = 15.5 Hz, 1H, $CH_2C{=}O$), 2.65 (m, 2H), 2.02 (m, 3H), 1.68 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 172.71 (p), 156.61 (p), 142.94 (p), 126.39 (ap), 125.44 (p), 118.67 (ap), 108.12 (ap), 71.45 (p), 55.33 (ap), 42.22 (p), 37.44 (ap), 35.77 (p), 35.28 (ap), 22.94 (p), 19.65 (p); MS M^+: 247. Anal. calcd. for $C_{15}H_{21}NO_3$: C 68.40%, H 8.04%, N 5.32%; found: C 68.32%, H 8.05%, N 5.20%.

3-Hydroxy-2,*N*,*N*-trimethyl-3-phenylpropionamides (18a and 18b)



A mixture of **18a** and **18b** (53 : 47, colorless oil): IR (CCl_4, cast): 3400 (br, md, OH), 1621 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H, phenyl), 5.12 (d, J = 2.3 Hz, 1H, C**H**OH, major), 4.79 (d, J = 6.8 Hz, 1H, C**H**OH, minor), 4.02 (br s, 2H, O**H**), 3.05 (pseudo quintet, J = ~7 Hz, 1H, CHC**H**CH_3), 3.02 (s, 3H, *N*-C**H**$_3$), 2.98 (s, 3H, *N*-C**H**$_3$), 2.87 (q x d, J_1 = 7.2 Hz, J_2 = 2.3 Hz, 1H, CHC**H**CH_3), 2.86 (s, 6H, *N*-C**H**3), 1.20 (d, J = 7.2 Hz, 3H, CHC**H**$_3$, minor), 1.04 (d, J = 7.2 Hz, 1H, CHC**H**$_3$, major); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 177.40 (p), 175.86 (p), 143.01 (p), 141.78 (p), 128.29 (ap), 128.12 (ap), 127.50 (ap), 127.11 (ap), 126.13 (ap), 126.03 (ap), 76.72 (ap), 73.23 (ap), 42.63 (ap), 41.58 (ap), 15.29 (ap), 9.59 (ap); MS M^+: 207.

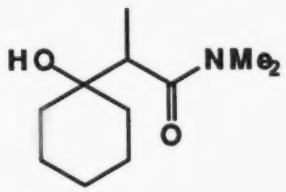
1-(1'-(*N*,*N*-Dimethylcarbamoyl)ethyl)cyclopentanol (19)



Compound **19** (colorless oil): IR (CH_2Cl_2, cast): 3395 (br, md, OH), 1621 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 4.07 (br s, 1H, hydroxy), 3.08 (s,

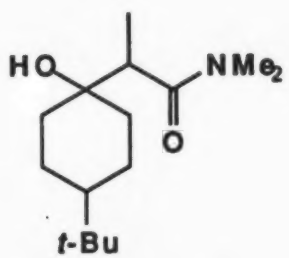
3H, *N*-CH_3), 2.97 (s, 3H, *N*-CH_3), 2.62 (q, J = 7.0 Hz, 1H, CH_3CH), 1.81 (m, 4H), 1.59 (m, 2H), 1.37(m, 2H),1.24 (d, J = 7.0 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 177.82 (p), 82.30 (p), 42.86 (ap), 40.48 (p), 37.62 (p), 37.43 (ap), 35.22 (ap), 23.94 (p), 23.76 (p), 13.00 (p); HRMS M^+: 185.1419 (calcd. for $C_{10}H_{19}NO_2$: 185.1416).

1-(1'-(*N,N*-Dimethylcarbamoyl)ethyl)cyclohexanol (20)



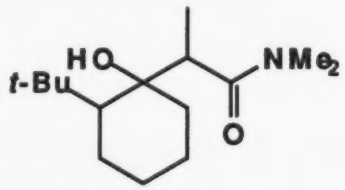
Compound **20** (white, low melting solid): IR (CCl_4, cast): 3380 (br, md, OH), 1619 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (br s, 1H, OH), 3.10 (s, 3H, *N*-CH_3), 2.98 (s, 3H, *N*-CH_3), 2.66 (q, J = 7.0 Hz, 1H, $CH_3CHC{=}O$), 1.65 (m, 5H), 1.40 (m, 2H), 1.20 (m, 3H), 1.16 (d, J = 7.0 Hz, 3H, $CH_3CHC{=}O$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 177.98 (p), 71.35 (p), 41.84 (ap), 37.52 (p), 34.61 (p),25.86 (p), 22.03 (p), 21.59 (p), 11.17 (ap); MS M^+: 199.

4-*tert*-Butyl-1-(1'-(*N,N*-dimethylcarbamoyl)ethyl)cyclohexanols (21a and 21b)



Compounds **21a** and **21b** (2.5 : 1, white crystals): mp 96.5 - 98.0 °C; IR (CCl_4, cast): 3380 (br, w, OH), 1621 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ for the major isomer: 4.15 (br s, 1H, OH), 3.07 (br s, 3H, *N*-CH_3), 2.98 (br s, 3H, *N*-CH_3), 2.52 (q, J = 7.0 Hz, 1H, $CHCH_3$), 1.18 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.86 (s, 9H, *t*-Butyl); for the minor isomer: 4.15 (br s, 1H, OH), 3.12 (br s, 3H, *N*-CH_3), 3.07 (q, J = 7.0 Hz, 1H, $CHCH_3$), 2.99 (br s, 3H, *N*-CH_3), 1.17 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.87 (s, 9H, *t*-Butyl); MS M^+: 255. Anal. calcd. for $C_{15}H_{29}NO_2$: C 70.54%, H 11.45%, N 5.48%; found: C 70.47%, H 11.24%, N 5.42%.

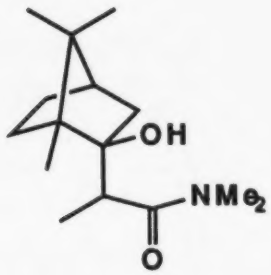
2-*tert*-Butyl-1-(1'-(*N,N*-dimethylcarbamoyl)ethyl)cyclohexanols (22a and 22b)



Compounds **22a** and **22b** (72 : 28, white crystals): IR ($CHCl_3$, cast): 3338 (br, st, OH), 1619 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ for the major isomer: 3.34 (q, J = 7.0 Hz, 1H, $CHCH_3$), 3.12 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3), 1.12 (d, J = 7.0 Hz, $CHCH_3$), 1.12 (s, 9H, *t*-butyl); for the minor one: 3.20 (q, J = 7.0 Hz, 1H, $CHCH_3$), 3.12 (s, 3H, NCH_3), 2.96 (s, 3H, NCH_3), 1.18 (d, J = 7.0 Hz, $CHCH_3$), 1.15 (s, 9H, *t*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 178.78 (p), 178.41 (p), 76.87 (p), 76.52 (p), 50.37 (ap), 45.34 (ap), 38.56 (ap), 38.01 (ap), 37.57 (ap), 35.59 (ap), 35.47 (ap), 34.95 (p), 34.48 (p), 32.61 (ap), 32.33 (ap), 30.76 (p), 27.08 (p), 26.11 (p), 23.68 (p), 22.86 (p), 22.06 (p), 21.53 (p),

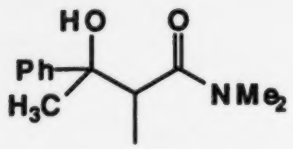
12.06 (ap), 11.45 (ap); MS M^+: 255. Anal. calcd. for $C_{15}H_{29}NO_2$: C 70.54%, H 11.45%, N 5.48%; found: C 70.27%, H 11.32%, N 5.45%.

(1R,2S,4R)-2-(1'-(*N,N*-Dimethylcarbamoyl)ethyl)borneols (23a and 23b)



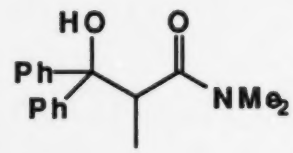
Compounds **23a** and **23b** (95 : 5, white crystals): mp 99.0 - 101.0 °C (for the major isomer, EtOH - hexanes); IR (CCl_4, cast): 3340 (br, md, OH), 1619 cm^{-1} (st, C=O); ^1H NMR (500 MHz, $CDCl_3$): δ for the major isomer: 4.5 (br s, 1H, O**H**), 3.10 (s, 3H, *N*-C**H**$_3$), 2.98 (s, 3H, *N*-C**H**$_3$), 2.88 (q, J = 7.0 Hz, C**H**CH$_3$), 2.12 (dt, J_1 = 13.0 Hz, J_2 = 3.7 Hz, 1H), 1.75 (m, 1H), 1.67 (t, J = 4.7 Hz, 1H), 1.48 (m, 1H), 1.35 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H, CHC**H**$_3$), 1.15 (s, 3H, CH$_3$), 1.06 (d, J = 13.0 Hz, 1H), 0.99 (s, 3H, CH$_3$), 0.95 (m, 1H), 0.84 (s, 3H, CH$_3$); for the minor isomer: 4.5 (br s, 1H, O**H**), 3.12 (s, 3H, *N*-C**H**$_3$), 2.96 (s, 3H, *N*-C**H**$_3$), 2.71 (q, J = 7.0 Hz, C**H**CH$_3$), 1.23 (d, J = 7.0 Hz, 3H, CHC**H**$_3$), 1.09 (s, 3H, CH$_3$), 0.81 (s, 3H, CH$_3$), 0.75 (s, 3H, CH$_3$); MS M^+: 253.

3-Hydroxy-2,*N,N*-trimethyl-3-phenylbutyramides (24a and 24b)



Compounds **24a** and **24b** (62 : 38, colorless oil): IR (CCl_4, cast): 3340 (br, md, OH), 1618 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ for the major one: 7.3 (m, 5H, phenyl), 5.52 (br s, 1H, OH), 3.18 (q, J = 7.0 Hz, 1H, $CHCH_3$), 2.79 (s, 3H, *N*-CH_3), 2.64 (s, 3H, *N*-CH_3), 1.46 (s, 3H, CCH_3), 1.34 (d, J = 7.0 Hz, $CHCH_3$); for the minor isomer: 7.3 (m, 5H, phenyl), 5.52 (br s, 1H, OH), 3.14 (s, 3H, *N*-CH_3), 3.03 (s, 3H, *N*-CH_3), 3.01 (q, J = 7.0 Hz, 1H, $CHCH_3$), 1.52 (s, 3H, CCH_3), 0.88 (d, J = 7.0 Hz, $CHCH_3$); ^{13}C NMR APT for the major isomer (75 MHz, $CDCl_3$): δ 177.73 (p), 146.04 (p), 128.05 (ap), 126.43 (ap), 124.95 (ap), 74.76 (p), 43.85 (ap), 37.71 (ap), 35.56 (ap), 30.01 (ap), 12.60 (ap); CIMS: 222 (M^+ + 1). Anal. calcd. for $C_{13}H_{19}NO_2$: C 70.54%, H 8.66%, N 6.33%; found: C 70.19%, H 8.59%, N 6.12%.

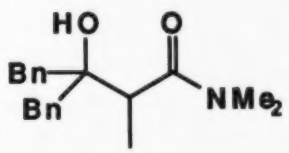
3-Hydroxy-2,*N*,*N*-trimethyl-3,3-diphenylpropionamide (25)



Compound **25** (white crystals, ethanol - hexanes): mp 117.0 - 118.5 °C; IR (CCl_4, cast): 3300 (br, md, OH), 1618 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (m, 4H, phenyl), 7.27 (m, 4H, phenyl), 7.15 (m, 2H, phenyl), 3.76 (q, J = 7.0 Hz, 1H, $CHCH_3$), 3.15 (s, 3H, *N*-CH_3), 2.80 (s, 3H, *N*-CH_3), 1.13 (d, J

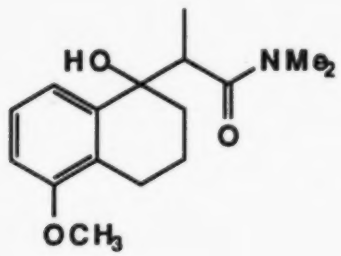
= 7.0 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 177.29 (p), 148.33 (p), 144.96 (p), 128.14 (ap), 128.05 (ap), 126.54 (ap), 126.42 (ap), 125.56 (ap), 125.17 (ap), 78.74 (p), 41.76 (ap), 37.32 (ap), 35.35 (ap), 12.43 (ap); CIMS: 284 ($M^+ + 1$). Anal. calcd. for $C_{18}H_{21}NO_2$: C 76.30%, H 7.47%, N 4.94%; found: C 75.99%, H 7.85%, N 4.86%.

3,3-Dibenzyl-3-hydroxy-2,*N*,*N*-trimethylpropionamide (26)



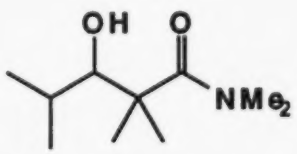
Compound **26** (white crystals, ethanol - hexanes): mp 98.0 - 99.0 °C; IR (CCl_4, cast): 3330 (br, md, OH), 1618 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 10H, phenyl), 3.17 (d, J = 14.0 Hz, 1H, CH_2Ph), 2.98 (d, J = 14.0 Hz, 1H, CH_2Ph), 2.87 (s, 3H, *N*-CH_3), 2.79 (d, J = 14.0 Hz, 1H, CH_2Ph), 2.67 (d, J = 14.0 Hz, 1H, CH_2Ph), 2.62 (s, 3H, *N*-CH_3), 2.60 (q, J = 7.2 Hz, 1H, $CHCH_3$), 1.27 (d, J = 7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 177.19 (p), 138.17 (p), 137.72 (p), 130.82 (ap), 130.34 (ap), 128.10 (ap), 128.00 (ap), 126.30 (ap), 126.25 (ap), 76.36 (p), 44.02 (p), 42.21 (p), 39.86 (ap), 37.07 (ap, in acetone-d_6), 35.11 (ap, in acetone-d_6), 12.48 (ap); HRMS: 293.1778 ($M^+ - H_2O$, calcd. for $C_{20}H_{23}NO$: 293.1780). Anal. calcd. for $C_{20}H_{25}NO_2$: C 77.14%, H 8.09%, N 4.50%; found: C 76.97%, H 8.22%, N 4.43%.

1-(1'-(*N,N*-Dimethylcarbamoyl)ethyl)-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalenes (27a and 27b)



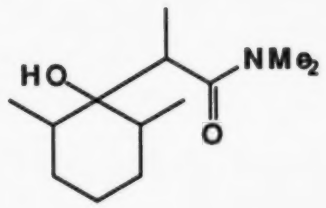
Compounds **27a** and **27b** (85 : 15, white crystals): IR (KBr): 3343 (br, st, OH), 1613 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ for the major isomer: 7.09 (t, J = 7.7 Hz, 1H, aromatic proton), 6.90 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H, aromatic proton), 6.69 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H, aromatic proton), 3.79 (s, 3H, OCH_3), 3.12 (q, J = 6.9 Hz, 1H, $CHCH_3$), 2.80 (s, 3H, *N*-CH_3), 2.31 (s, 3H, *N*-CH_3), 1.21 (d, J = 6.9 Hz, $CHCH_3$); for the minor isomer: 7.35 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H, aromatic proton), 7.19 (t, J = 7.7 Hz, 1H, aromatic proton), 6.74 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H, aromatic proton), 3.81 (s, 3H, OCH_3), 3.05 (s, 3H, *N*-CH_3), 3.00 (s, 3H, *N*-CH_3), 1.13 (d, J = 6.9 Hz, $CHCH_3$); MS M^+: 277. Anal. calcd. for $C_{16}H_{23}NO_3$: C 69.29%, H 8.36%, N 5.05%; found: C 68.93%, H 8.65%, N 4.98%.

3-Hydroxy-2,2,4,*N,N*-pentamethylvaleramide (32)



Compound **32** (white crystals, ethanol - hexanes): mp 85.5 - 86.0 °C; IR (CCl_4, cast): 3404 (st, OH), 1597 cm^{-1} (st, C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (br s, 1H, OH), 3.37 (d, J = 3.2 Hz, 1H, CHCHOH), 3.02 (s, 6H, N-CH_3), 1.88 (d of heptets, J_1 = 7.0 Hz, J_2 = 3.2 Hz, 1H, Me_2CHCH), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 0.99 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.87 (d, J = 7.0 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 178.81 (p), 83.44 (ap), 45.91 (p), 38.56 (ap), 29.55 (ap), 24.29 (ap), 22.94 (ap), 22.81 (ap), 17.23 (ap); MS M^+: 187. Anal. calcd. for $C_{10}H_{21}NO_2$: C 64.13%, H 11.30%, N 7.48%; found: C 63.93%, H 11.20%, N 7.32%.

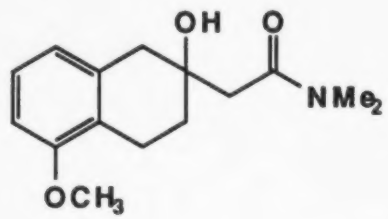
1-(1'-(*N,N*-Dimethylcarbamoyl)ethyl)-2,6-dimethylcyclohexanol (33)



Compound **33** (only one isomer observed in the ^1H NMR spectrum, white crystals, ethanol - hexanes): mp 81.5 - 82.0 °C; IR (CCl_4, cast): 3343 (br, md, OH), 1619 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 4.40 (br s, 1H, OH), 3.34 (q, J = 7.0 Hz, 1H, CH_3CHC=O), 3.12 (s, 3H, NCH_3), 2.96 (s, 3H, NCH_3), 1.96 (m, 1H), 1.70 (m, 2H), 1.48 (m, 4H), 1.28 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H, $CHCH_3$), 1.09 (d, J = 7.2 Hz, 3H, $CHCH_3$), 1.08 (d, J = 7.1 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 178.31 (p), 75.37 (p), 38.29 (ap), 37.78 (ap), 33.59 (ap), 30.53 (p), 29.69 (p), 17.09 (p), 16.31 (ap), 15.46 (ap), 12.44 (ap); HRMS M^+: 227.1888 (calcd. for $C_{13}H_{25}NO_2$: 127.1885). Anal. calcd. for

$C_{13}H_{25}NO_2$: C 68.68%, H 11.08%, N 6.16%; found: C 68.86%, H 11.22%, N 6.24%.

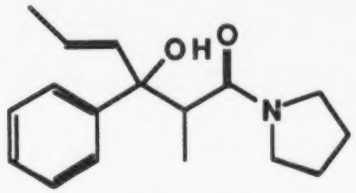
2-(Dimethylcarbamoylmethyl)-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (34)



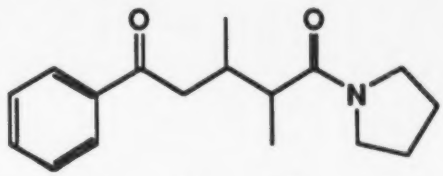
Compound **34** (white crystals, ethanol - hexanes): mp 114.5 - 115.5 °C; IR (CCl_4, cast): 3360 (br, md, OH), 1623 (st, C=O), 1257 cm^{-1} (st, C-O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (pseudo t, $J_1 = J_2 = 7.9$ Hz, 1H, aromatic proton), 6.68 (d, J = 7.5 Hz, 1H, aromatic proton), 6.67 (d, J = 8.1 Hz, 1H, aromatic), 4.67 (br s, 1H, O**H**), 3.82 (s, 3H, OCH_3), 2.97 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 3.05 - 2.80 (m, 3H, benzylic), 2.63 (dt, $J_1 = 18.2$ Hz, $J_2 = 7.0$ Hz, 1H, benzylic), 2.50 (s, 2H, $CH_2C{=}O$), 1.99 (dddd, $J_1 = 2J_2 = 2J_3 = 14.0$ Hz, $J_4 = 0.8$ Hz, 1H, CH_2CH_2COH), 1.86 (dddd, $J_1 = 2J_2 = 2J_3 = 13.2$ Hz, $J_4 = 1.3$ Hz, 1H, CH_2CH_2COH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 172.72 (p), 157.20 (p), 136.12 (p), 126.41 (ap), 124.03 (p), 121.69 (ap), 107.19 (ap), 69.39 (p), 55.22 (ap), 42.16 (p), 39.88 (p), 37.38 (ap), 35.20 (ap), 33.91 (p), 20.98 (p); HRMS M^+: 263.1514 (calcd. for $C_{15}H_{21}NO_3$: 263.1521). Anal. calcd. for $C_{15}H_{21}NO_3$: C 68.42%, H 8.04%, N 5.32%; found: C 68.08%, H 8.10%, N 5.15%.

(*E*,2'*R,3'*R**)- and (*E*, 2'*R**,3'*S**)-1-(3'-Hydroxy-2'-methyl-1'-oxo-3'-phenyl-4'-hexenyl)pyrrolidine (40a and 40b) and (2'*R**,3'*R**)- and**

(2'R^*,3'S^*)-1-(2',3'-dimethyl-1',5'-dioxo-5'-phenylpentyl)pyrrolidine (41a and 41b)



40a, 40b



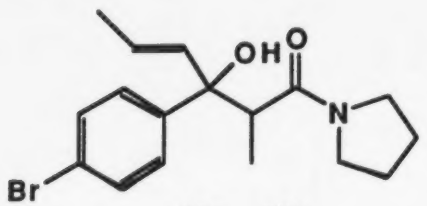
41a, 41b

Compounds **40a** and **40b** (an inseparable mixture, about 1 : 1): IR ($CDCl_3$, cast): 3320 (br, md, OH), 1613 cm^{-1} (st, C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10H, phenyl), 5.95 - 5.55 (m, 4H, olefinic protons), 3.65 - 3.10 (m, 8H, NCH_2CH_2), 3.10 (two q, J = 7.0 Hz, 2H, $CHCH_3$), 2.15 - 1.75 (m, 8H, NCH_2CH_2), 1.72 (d x d, J_1 = 6.2 Hz, J_2 = 1.7 Hz, 3H, $CH=CHCH_3$), 1.65 (d, J = 5.2 Hz, 3H, $CH=CHCH_3$), 1.28 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.93 (d, J = 7.0 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 175.63 (p), 175.29 (p), 147.27 (p), 144.13 (p), 136.89 (ap), 133.78 (ap), 128.09 (ap), 127.99 (ap), 126.47 (ap, two carbons, 126.89 and 126.85 in acetone-d_6), 125.33 (ap), 125.16 (ap), 124.89 (ap), 123.97 (ap), 77.58 (p, in acetone-d_6), 47.01 (p), 46.52 (p), 45.61 (p), 45.34 (ap), 45.21 (p), 45.15 (ap), 26.08 (p), 25.81 (p), 24.39 (p), 24.09 (p), 17.82 (ap), 12.32 (ap), 11.96 (ap); HRMS M^+: 273.1724 (calcd. for $C_{17}H_{23}NO_2$: 273.1729).

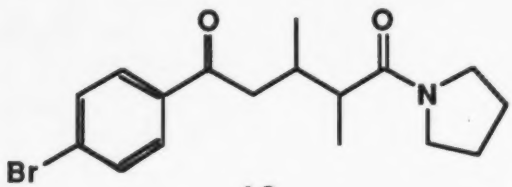
Compounds **41a** and **41b** (an inseparable mixture, 90 : 10): IR ($CDCl_3$, cast): 1680 (st, ketone C=O), 1633 cm^{-1} (st, amide C=O); ^1H NMR for the major isomer (200 MHz, $CDCl_3$): δ 8.00 (m, 2H, phenyl), 7.47 (m, 3H, phenyl), 3.47 (m, 4H, NCH_2CH_2), 3.21 (dd, J_1 = 15.4 Hz, J_2 = 4.6 Hz, 1H, CH_2CH), 2.71 (dd, J_1 = 15.4 Hz, J_2 = 8.2 Hz, 1H, CH_2CH), 2.65 - 2.40 (m, 2H), 1.87 (m, 4H, NCH_2CH_2

), 1.13 (d, J = 6.8 Hz, 3H, $CHCH_3$), 0.99 (d, J = 6.8 Hz, 3H, $CHCH_3$); HRMS M+: 273.1733 (calcd. for $C_{17}H_{23}NO_2$: 273.1729).

(*E*,2'*R,3'*R**)- and (*E*, 2'*R**,3'*S**)-1-(3'-(4-Bromophenyl)-3'-hydroxy-2'-methyl-1'-oxo-4'-hexenyl)pyrrolidine (42a and 42b) and 1-(5'-(4-bromophenyl)-2',3'-dimethyl-1',5'-dioxopentyl)pyrrolidine (43)**



42a, 42b



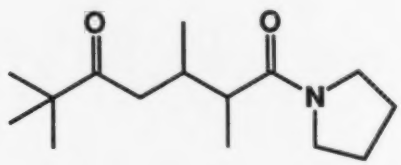
43

Compounds **42a** and **42b** (an inseparable mixture, about 1 : 1): IR (KBr): 3288 (br, md, OH), 1613 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 - 7.25 (m, 8H, aromatic protons), 6.19 (s, 1H, OH), 6.17 (s, 1H, OH), 5.85 - 5.45 (m, 4H, olefinic protons), 3.60 - 3.00 (m, 8H, NCH_2CH_2), 2.97 (q, J = 7.0 Hz, 1H, $CH_3CHC{=}O$), 2.90 (q, J = 7.0 Hz, 1H, $CH_3CHC{=}O$), 2.05 - 1.55 (m, 8H, NCH_2CH_2), 1.67 (dd, J_1 = 6.6 Hz, J_2 = 1.6 Hz, 3H, $CH{=}CHCH_3$), 1.62 (d, J = 5.0 Hz, 3H, $CH{=}CHCH_3$), 1.26 (d, J = 7.0 Hz, 3H, $CH_3CHC{=}O$), 0.89 (d, J = 7.0 Hz, 3H, $CH_3CHC{=}O$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 175.18 (p), 174.96 (p), 146.49 (p), 143.20 (p), 136.27 (ap), 133.30 (ap), 131.00 (ap), 130.91 (ap), 127.17 (ap), 126.69 (ap), 125.32 (ap), 124.30 (ap), 120.28 (p), 120.19 (p), 76.80 (p), 76.65 (p), 46.87 (p), 46.44 (p), 45.50 (p), 45.14 (p), 44.86 (ap), 44.67 (ap), 25.90 (p), 25.68 (p), 24.21 (p), 23.96 (p), 17.67 (ap), 12.14 (ap), 11.78 (ap); HRMS M+: 353.0794 (calcd. for $C_{17}H_{22}{}^{81}BrNO_2$: 353.0813), 351.0834 (calcd.

for $C_{17}H_{22}{}^{79}BrNO_2$: 351.0834). Anal. calcd. for $C_{17}H_{22}BrNO_2$: C 57.96%, H 6.29%, N 3.98%, Br 22.68%; found: C 57.79%, H 6.19%, N 3.85%, Br 22.83%.

Compound **43** (only one isomer observed in the ^1H NMR spectrum): IR (KBr): 1680 (st, ketone C=O), 1632 cm^{-1} (st, amide C=O); ^1H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H, aromatic), 7.57 (m, 2H, aromatic), 3.42 (m, 4H, NCH_2CH_2), 3.17 (dd, J_1 = 15.2 Hz, J_2 = 4.4 Hz, 1H, CH_2CHCH), 2.60 (dd, J_1 = 15.2 Hz, J_2 = 8.7 Hz, 1H, CH_2CHCH), 2.52 (pseudo quintet, J = 6.8 Hz, 1H, CH_2CHCH), 2.41 (m, 1H, CH_2CHCH), 2.00 - 1.75 (m, 4H, NCH_2CH_2), 1.09 (d, J = 6.8 Hz, 3H, $CHCH_3$), 0.94 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.61 (p), 174.43 (p), 135.70 (p), 131.90 (ap), 130.00 (ap), 128.15 (p), 46.69 (p), 45.76 (p), 43.80 (p), 42.82 (ap), 32.94 (ap), 26.20 (p), 24.33 (p), 16.69 (ap), 14.54 (ap); HRMS M^+: 353.0825 (calcd. for $C_{17}H_{22}NO_2{}^{81}Br$: 353.0813), 351.0839 (calcd. for $C_{17}H_{22}NO_2{}^{79}Br$: 351.0834).

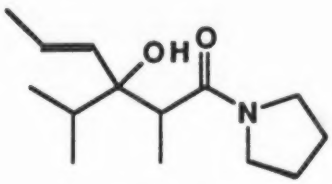
(2'R^*,3'R^*)- and (2'R^*,3'S^*)-1-(1',5'-Dioxo-2',3',6',6'-tetramethylheptyl)pyrrolidine (44a and 44b)



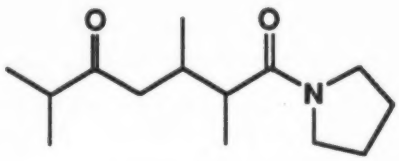
In the ^1H NMR spectrum, no 1,2-adduct was observed. Compounds **44a** and **44b** (an inseparable mixture, about 1 : 1): IR (CCl_4, cast): 1704 (st, ketone), 1646 cm^{-1} (st, amide); ^1H NMR (200 MHz, $CDCl_3$): δ 3.45 (br m, 8H, NCH_2CH_2), 2.8 - 2.2 (m, 8H), 1.85 (br s, 8H, NCH_2CH_2), 1.09 (s, 18H, *t*-butyl), 1.07 (d, J = 7.0 Hz, 3H, $CHCH_3$), 1.06 (d, J = 7.0 Hz, 3H, $CHCH_3$), 0.93 (d, J = 6.7 Hz, 3H, $CHCH_3$), 0.92 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ

215.49 (p), 174.56 (p), 46.60 (p), 45.64 (p), 44.25 (p), 41.88 (ap), 41.24 (ap), 40.83 (p), 39.03 (p), 33.13 (p), 31.03 (ap), 30.95 (ap), 26.36 (ap), 26.20 (ap), 26.11 (p), 24.26 (p), 18.45 (ap), 16.34 (ap), 13.19 (ap), 13.10 (ap); MS M+: 253.

(*E*,2'*R,3'*R**)- and (*E*, 2'*R**,3'*S**)-1-(3'-Hydroxy-2'-methyl-3'-isopropyl-1'-oxo-4'-hexenyl)pyrrolidine (45a and 45b) and (2'*R**,3'*R**)- and (2'*R**,3'*S**)-1-(1',5'-dioxo-2',3',6'-trimethylheptyl)-pyrrolidine (46a and 46b)**



45a, 45b



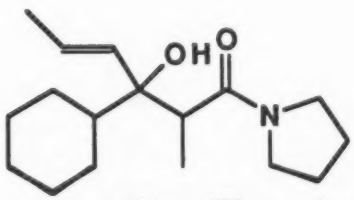
46a, 46b

Two separable 1,2-adducts (**45a** and **45b**) were isolated in a ratio of 37 : 63. The first (minor) 1,2-adduct: IR (KBr): 3332 (br, md, OH), 1608 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (dq, J_1 = 15.3 Hz, J_2 = 6.5 Hz, 1H, CH=C**H**CH_3), 5.15 (br s, 1H, **OH**), 5.11 (dq, J_1 = 15.3 Hz, J_2 = 1.6 Hz, 1H, C**H**=$CHCH_3$), 3.44 (m, 4H, NCH_2CH_2), 2.64 (q, J = 7.1 Hz, 1H, CH_3C**H**C=O), 1.90 (m, 5H, NCH_2CH_2 and Me_2C**H**), 1.71 (dd, J_1 = 6.5 Hz, J_2 = 1.6 Hz, 3H, CH=CHC**H**$_3$), 1.09 (d, J = 7.1 Hz, 3H, C**H**$_3$CHC=O), 0.84 (d, J = 6.7 Hz, 3H, C**H**$_3$CHCOH), 0.80 (d, J = 7.0 Hz, 3H, C**H**$_3$CHCOH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 176.55 (p), 129.11 (ap), 125.45 (ap), 78.37 (p), 46.67 (p), 45.53 (p), 40.98 (ap), 36.51 (ap), 26.08 (p), 24.33 (p), 18.43 (ap), 17.93 (ap), 17.41 (ap), 12.84 (ap); HRMS M+: 239.1886 (calcd. for $C_{14}H_{25}NO_2$: 239.1885). The second 1,2-adduct: IR (KBr): 3339 (br, md, OH), 1616 cm^{-1} (st, C=O); ^1H NMR

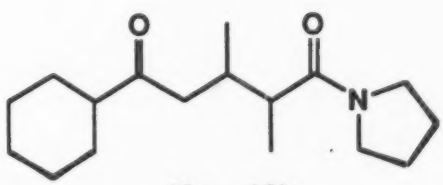
(360 MHz, $CDCl_3$): δ 5.67 (dq, J_1 = 15.3 Hz, J_2 = 6.5 Hz, 1H, CH=**CH**CH_3), 5.48 (br s, 1H, **OH**), 5.34 (dq, J_1 = 15.3 Hz, J_2 = 1.5 Hz, 1H, **CH**=$CHCH_3$), 3.42 (m, 4H, NCH_2CH_2), 2.73 (q, J = 7.0 Hz, 1H, CH_3CHC=O), 1.85 (m, 5H, NCH_2CH_2 and Me_2CH), 1.65 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz, 3H, CH=CHCH_3), 1.15 (d, J = 7.0 Hz, 3H, CH_3CHC=O), 0.82 (d, J = 6.5 Hz, 3H, CH_3CHCOH), 0.81 (d, J = 6.6 Hz, 3H, CH_3CHCOH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 176.06 (p), 131.34 (ap), 125.94 (ap), 77.23 (p), 46.89 (p), 45.42 (p), 41.25 (ap), 32.84 (ap), 26.04 (p), 24.36 (p), 17.88 (ap), 17.13 (ap), 16.60 (ap), 10.70 (ap); HRMS M^+: 239.1884 (calcd. for $C_{14}H_{25}NO_2$: 239.1885).

Compounds **46a** and **46b** (an inseparable mixture, about 90 : 10): IR (KBr): 1736 (md, ketone C=O), 1708 (ketone, C=O), 1637 cm^{-1} (st, amide C=O); ^{1}H NMR for the major isomer (400 MHz, $CDCl_3$): δ 3.80 - 3.35 (m, 4H, NCH_2CH_2), 2.65 - 2.15 (m, 5H, α-protons of the ketone and the amide, and CH_2CHCH_3), 1.07 (d, J = 6.8 Hz, 3H, CH_3CHC=O), 1.06 (d, J = 6.9 Hz, 6H, $CHMe_2$), 0.92 (d, J = 7.0 Hz, 3H, CH_2CHCH_3); HRMS M^+: 239.1876 (calcd. for $C_{14}H_{25}NO_2$: 239.1885).

(*E*,2'*R,3'*R**)- and (*E*, 2'*R**,3'*S**)-1-(3'-Cyclohexyl-3'-hydroxy-2'-methyl-1'-oxo-4'-hexenyl)pyrrolidine (47a and 47b) and (2'*R**,3'*R**)- and (2'*R**,3'*S**)-1-(5'-cyclohexyl-2',3'-dimethyl-1',5'-dioxopentyl)-pyrrolidine (48a and 48b)**



47a, 47b



48a, 48b

Two 1,2 -adducts (**47** and **47b**) were isolated in pure forms in a ratio of 40 : 60. The first one (the minor one, white crystals, ether - hexane): mp 153.0 - 154.5 °C; IR ($CDCl_3$, cast): 3335 (br, md, OH), 1602 cm^{-1} (st, C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (dq, J_1 = 15.2 Hz, J_2 = 7.2 Hz, 1H, CH_3CH=CH), 5.12 (dq, J_1 = 15.2 Hz, J_2 = 1.8 Hz, 1H, CH_3CH=C**H**), 3.48 (m, 4H, NCH_2CH_2), 2.64 (q, J = 7.1 Hz, 1H, C**H**CH_3), 1.92 (m, 5H), 1.72 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 3H, CH_3CH=CH), 1.55 (m, 3H),1.09 (d, J = 7.1 Hz, 3H, CHC**H**$_3$), 1.05 (m, 5H); ^{13}C NMR APT (100 MHz, $CDCl_3$): δ 176.56 (p), 130.49 (ap), 125.63 (ap), 78.06 (p), 47.26 (ap), 46.64 (p), 45.47 (p), 40.69 (ap), 28.88 (p), 27.18 (p), 26.99 (p), 26.63 (p), 26.36 (p), 26.07 (p), 24.32 (p), 17.90 (ap), 12.61 (ap); MS M^+: 279. Anal. calcd. for $C_{17}H_{29}NO_2$: C 73.07%, H 10.46%, N 5.01%; found: C 72.93%, H 10.17%, N 4.98%. The second one (the major one): IR ($CDCl_3$, cast): 3350 (br, md, OH), 1614 cm^{-1} (st, C=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.64 (dq, J_1 = 15.3 Hz, J_2 = 6.5 Hz, 1H, CH_3C**H**=CH)), 5.37 (dq, J_1 = 15.3 Hz, J_2 = 1.8 Hz, 1H, CH_3CH=C**H**), 3.41 (m, 4H, NCH_2CH_2), 2.73 (q, J = 7.1 Hz, C**H**CH_3), 2.00 - 1.55 (m, 9H), 1.63 (dd, J_1 = 6.5 Hz, J_2 = 1.8 Hz, 3H, CH=CHC**H**$_3$), 1.3 - 0.8 (m, 6H), 1.16 (d, J = 7.0 Hz, 3H, CHC**H**$_3$); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 175.91 (p), 132.54 (ap), 124.97 (ap), 76.68 (p), 46.74 (p), 45.24 (p), 43.23 (ap), 40.78 (ap), 27.11 (p), 26.60 (p), 26.47 (p), 26.38 (p), 26.19 (p), 25.87 (p), 17.64 (ap), 10.52 (ap); MS M^+: 279.

Compounds **48a** and **48b** (an inseparable mixture, 1 : 1): IR ($CDCl_3$, cast): 1705 (st, ketone), 1636 cm^{-1} (st, amide); ^1H NMR (400 MHz, $CDCl_3$): δ 3.45 (m, 4H, NCH_2CH_2), 2.60 - 2.30 (m, 6H), 1.80 (m, 7H), 1.22 (m, 5H), 1.05 (d, J = 6.8 Hz, 6H, CHC**H**$_3$ for both isomers), 0.91 (d, J = 6.8 Hz, 3H, CHC**H**$_3$ for one isomer), 0.89 (d, J = 6.8 Hz, 3H, CHC**H**$_3$ for the other isomer); MS M^+: 279.

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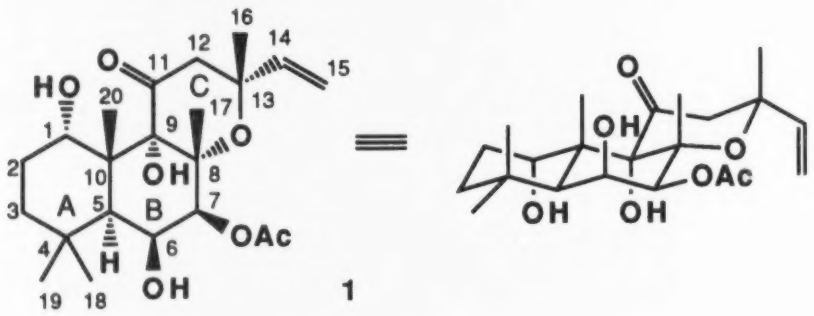
Chapter Two

Syntheses of Key Intermediates Towards Forskolin

Introduction

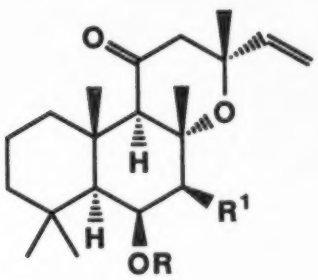
In two separate screening programs directed towards the discovery of new leads from Indian medicinal plants at Hoechst Pharmaceutical Research in Bombay[1-3] and Hoechst Pharmaceutical Research of the Central Drug Research Institute in Lucknow, India,[4] researchers isolated two compounds from the methanolic extract of *Coleus forskolii* Briq. They were responsible for the observed physiological activities of the extract and were given two different names, forskolin and coleonol, at these two institutions. Later, they discovered that these two compounds had the same identity, which was represented as compound **1**, a labdane diterpenoid. This structure was determined by a series of extensive chemical and spectroscopic investigations and was finally proved unequivocally by X-ray analysis.[5] It comprised about 0.1% of the dry weight of the root.



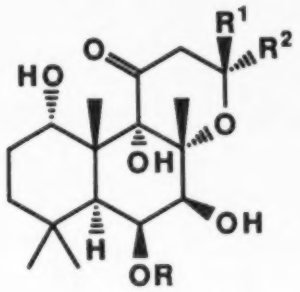
1

Also isolated from the methanolic and chloroform extracts of the powdered and dried roots of *Coleus forskolii* were 1,9-dideoxyforskolin (**2**),[1] its 7-deacetyl (**3**)[1] and 7-deacetoxy (**4**) analogs, 7-deacetylforskolin (**5**),[1] 6-acetyl-7-deacetylforskolin (**6**)[1,6] and its 13-epimer (**7**),[6] 9-deoxyforskolin (**8**) and its 13-epimer (**9**),[7] 11-ketomanoyl oxide and its hydroxy derivatives (**10-14**).[8-10] Biological oxidations of some of these analogs to the other ones of higher oxygenation states were also extensively studied,[11-13] especially the oxidation

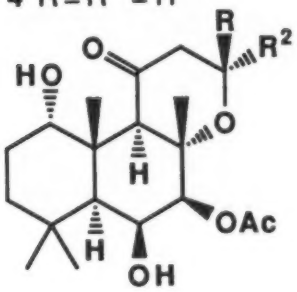
of 1,9-dideoxyforskolin, because of its equal or even higher abundance in *Coleus forskolii* . It was found that this compound could be converted to 9-deoxyforskolin and forskolin, among other products. The products and their yields varied, depending on the fungal strains and methods used.



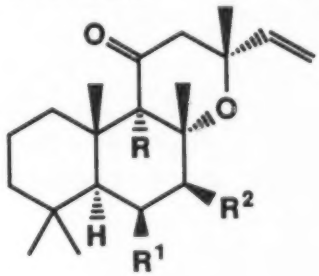
2 R = H, R^1 = OAc
3 R = H, R^1 = OH
4 R = R^1 = H



5 R = H, R^1 = Me, R^2 = -CH=CH_2
6 R = Ac, R^1 = Me, R^2 = -CH=CH_2
7 R = Ac, R^1 = -CH=CH_2, R^2 = Me



8 R = Me, R^1 = -CH=CH_2
9 R = -CH=CH_2, R^1 = Me



10 R = OH, R^1 = R^2 = H
11 R = R^1 = OH, R^2 = OAc
12 R = R^1 = R^2 = OH
13 R = R^1 = R^2 = H
14 R = R^1 = OH, R^2 = H

The biological activities can be classified into two general categories by their underlying mechanisms, namely the cyclic AMP dependent and independent ones.[14-16] Forskolin stimulates adenylate cyclase rapidly and reversibly *in vivo* and *in vitro*, hence increasing intracellular cAMP. It lowers

blood pressure, has potent positive inotropic activity, inhibits human platelet aggregation, decreases intraocular pressure, relaxes smooth muscles in lung and parenchymal tissues and reduces airway resistance. Thus, it could be used as anti-hypertension, anti-glaucoma, anti-platelet-aggregation and anti-asthma agents. But the broad action of forskolin in stimulating pharmacological phenomena associated with increase in cAMP in most tissues may, however, limit its clinical usefulness. Its specific enzyme activating property makes it a useful tool in the study of the pathophysiology of a variety of disorders related to modulation of adenylate cyclase. Thus, forskolin has become a very potent tool for studying the role of cAMP in regulating ion channels, metabolic pathways, cell growth, muscle contractions, secretory process, and for studying defects in the expression of a hormonal signal at the level of activated protein kinases or phosphorylated proteins.[17] Forskolin produces cAMP-independent effects through modulation of nicotinic acetylcholine receptor channel desensitization, modulation of voltage-dependent potassium channels, reversal of multi-drug resistance, and inhibition of glucose transport protein.

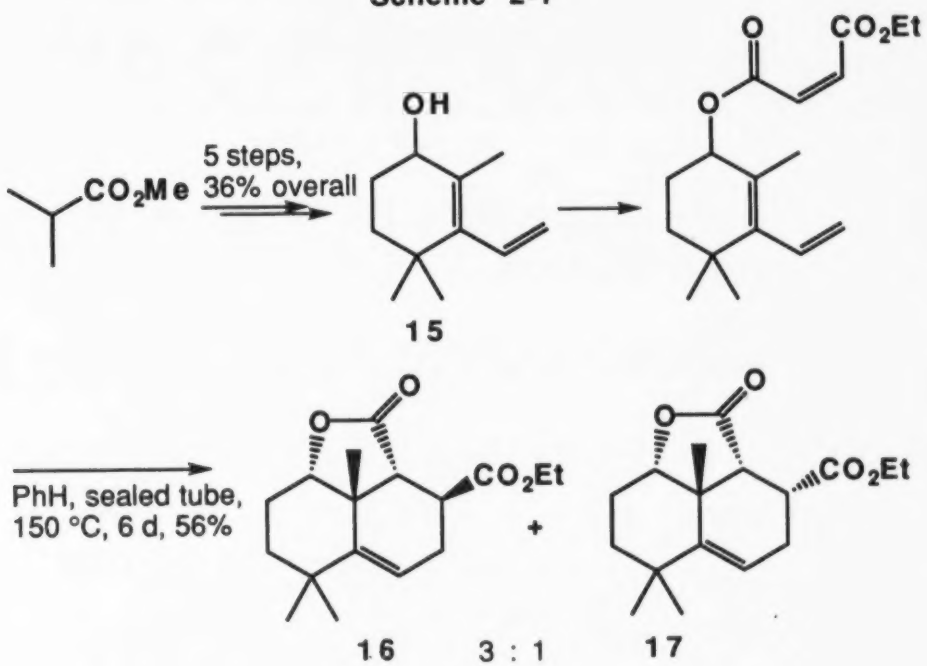
A careful look at the structure of forskolin reveals a highly functionalized and stereochemically complicated compound. It has eight stereogenic centers. Seven of them are contiguous and six of them located in ring B. In addition to three hydroxy groups, four methyl groups occupy axial positions. A tremendous amount of 1,3-diaxial interactions can be expected, making their introduction really interesting. Only one acetoxy group at C-7 lies in the equatorial position. In fact, under controlled acetylation of 7-deacetylforskolin, this was the only position that was acetylated. These unique and challenging structural features and biological properties have spurred a plethora of synthetic efforts towards the partial and total syntheses of this compound and its analogs. So far, three total syntheses have been accomplished (Ziegler, Ikegami and Corey).[18-20]

Numerous efforts have been devoted to the syntheses and elaboration of the B and C rings, and the enantioselective synthesis of forskolin and its derivatives. Earlier results have been reviewed.[16,21-23] The strategies and newer results will be discussed here, with focuses on (1) approaches towards the A-B ring decalin system, (2) syntheses and elaboration of the C ring, (3) direct formation of the A-B-C ring systems, (4) total syntheses, (5) advanced intermediates and (6) enantioselective preparation of key intermediates.

Approaches towards the A-B ring decalin system

The first few attempts toward the A-B ring system involved the intramolecular approach. Interestingly, all of the three published total syntheses took advantage of this cyclization method.[18-20]

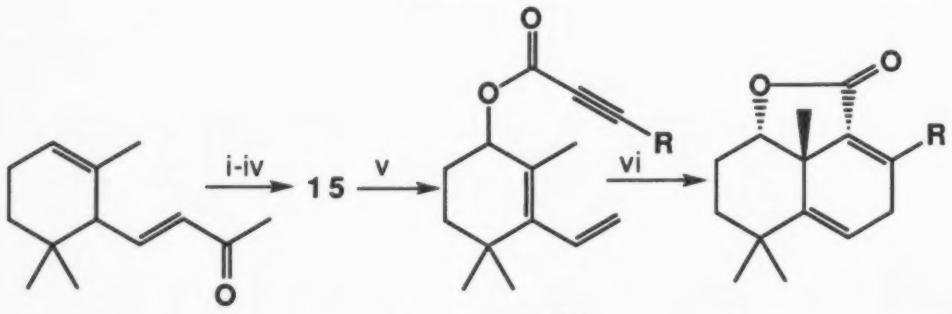
Scheme 2-1



Jenkins and co-workers started with a simple chemical compound, methyl isobutyrate, to establish the A ring and prepare the diene alcohol **15** (Scheme 2-1). Afterwards, a maleate appendage was added for the intramolecular Diels-Alder reaction. Thermal cyclization gave the *endo*-product **17** and the isomerized product **16** in a ratio of 1 : 3.[24]

Later, the readily available and cheap natural product, α-ionone, was used by Nicolaou *et al.* to establish the A-ring and prepare **15** (Scheme 2-2).[25] A doubly activated acetylene rather than a double bond was used. The trimethylsilyl group proved to be the most efficient activator, offering 92% yield after the diene-acetylene assembly was heated in a sealed tube at 140 °C for 24 hr. Simple and unactivated ether appendage was used by Liu and co-workers[26] to produce the Diels-Alder adduct under more drastic conditions (Scheme 2-3).

Scheme 2-2

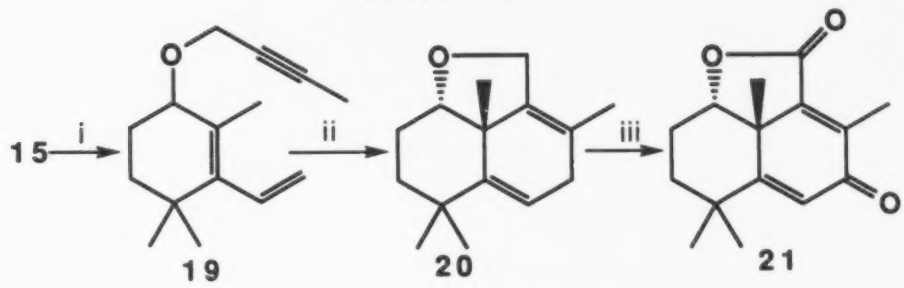


18

R = TMS, H, Me, COOMe

i. MCPBA, CH_2Cl_2, -78 °C to 0 °C, 12 hr; 95%, ii. O_3, CH_2Cl_2, MeOH, -78 °C, Me_2S, -78 °C to 25 °C; iii. DBU, 0 °C to 25 °C, 90%; iv. $Ph_3P^+MeCl^-$, BuLi, THF, 0 °C, 96%; v. TMSC≡CCO_2H, DCC, DMAP, CH_2Cl_2, 0 °C to 25 °C, 90%; vi. sealed tube, heat.

Scheme 2-3

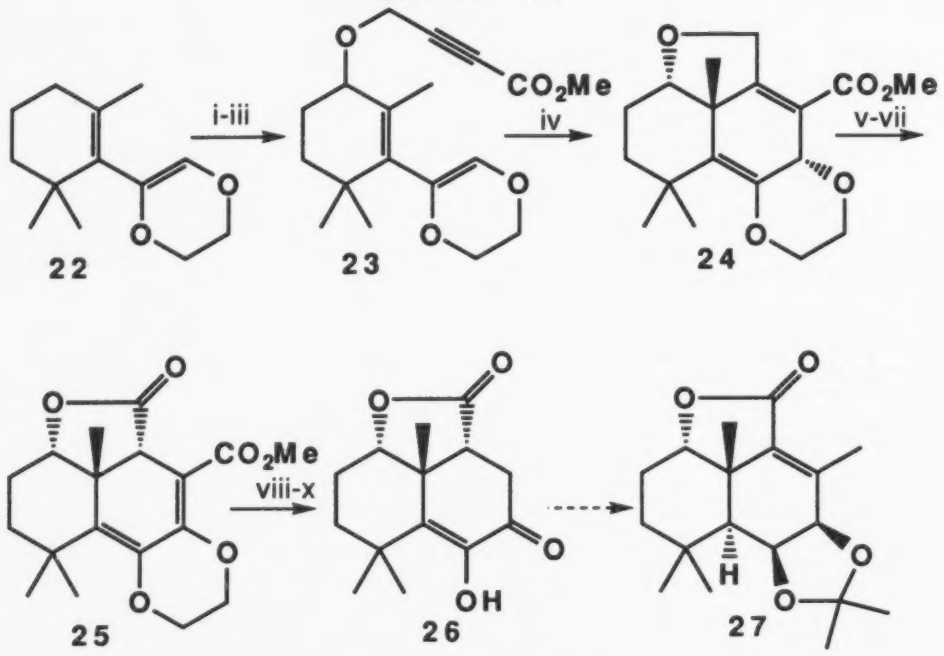


i. NaOH, H_2O, Bu_4NI, $BrCH_2C{\equiv}CMe$, 97%; ii. sealed tube, 160 °C, 3 d, 74%; iii. CrO_3 - 3,5-dimethylpyrazole, CH_2Cl_2, r.t., 95%.

A more recent attempt by Hanna and co-workers incorporated a 1,4-dioxene ring into the diene moiety to give a more functionalized product, which, as the authors believed, could be easily converted to a Ziegler intermediate **27**, as will be discussed later (Scheme 2-4).[27]

In the above discussed intramolecular approaches, the diene moieties made up the C_{10}-C_5-C_6-C_7 part of the decalin system. In the next two examples and later in Ikegami's total synthesis, a different combination was used. The four carbons from the diene constituted the C_5-C_6-C_7-C_8 portion of the decalin skeleton. Trost and co-workers prepared **28a-f** from crotyl alcohol and 4-formyl-4-methylvaleric acid (Scheme 2-5). It was found that under thermal condition, **28a** cyclized to afford **29** only in 75% yield. Under the catalysis of $EtAlCl_2$, **28b**, **28c** and **28f** gave only one product as **31**(30%), **30c** (80%) and **29f** (84%) respectively. Dienes **28d** and **28e** gave mixtures of **29**, **30** and **31**, with **29** as the major products.[28]

Scheme 2-4



i. Br_2, Na_2CO_3, CH_2Cl_2, -70 °C, 60%; ii. 60% aq NaOH, Bu_4NI (0.1 eq), propargylic bromide (3 eq), 83%; iii. BuLi (1.5 eq), THF, -70 °C; $ClCO_2Me$ (4 eq), -70 °C, 85%; iv. 140 °C, toluene, sealed tube, 85%; v. SeO_2 (2 eq), dioxane, reflux; vi. Ag_2CO_3 on celite, PhH, reflux (90%, two steps); vii. DBU, THF, reflux, 92%; viii. 70% aq $HClO_4$, CH_3CN, 60 °C, 72%; ix. Me_3SiCl (5 eq), NaI (5 eq), CH_3CN, 83%; x. Zn, NH_4Cl, EtOH, reflux, 92%.

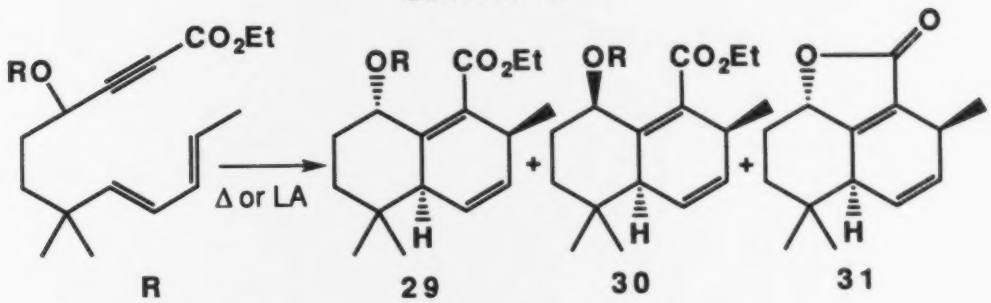
Recently Tsang and Fraser-Reid synthesized chiral tricyclic lactone **33** from 2,3,4,6-*O*-benzyl-glucono-1,5-lactone (Scheme 2-6). Compound **33**, on further oxidation and methanolysis, gave lactone **34**, which could be used to synthesize an intermediate in Ziegler's scheme.[29]

So far, intermolecular Diels-Alder reactions were less utilized and less successful in constructing the A-B ring systems of forskolin and its analogs. No effort has resulted in any partial or total synthesis of forskolin.

Snider *et al.* utilized the cyclopropyl derivative **35** instead of the more congested, less reactive dimethyl analog to cyclize with a doubly activated

dienophile **36** (Scheme 2-7). Still, the yield was only 38%. Hence continuation of this route to forskolin was prevented.[30]

Scheme 2-5

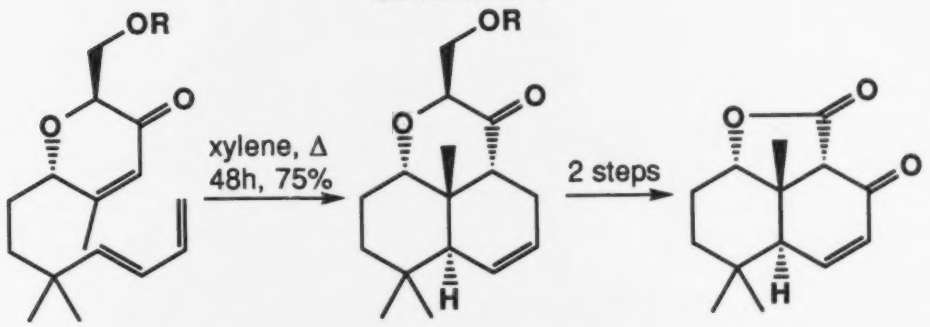


R

28a H
28b TMS
28c TBDMS
28d CONHPh
28e MOM
28f CO ^{t}Bu

29 **30** **31**

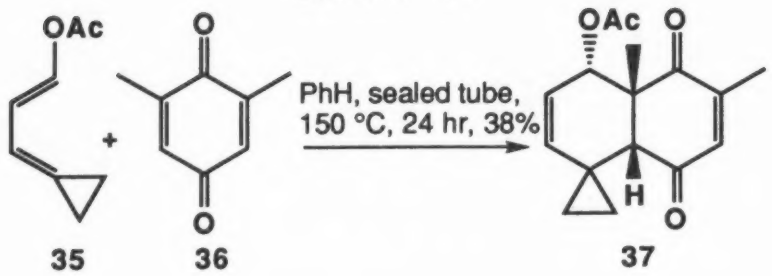
Scheme 2-6



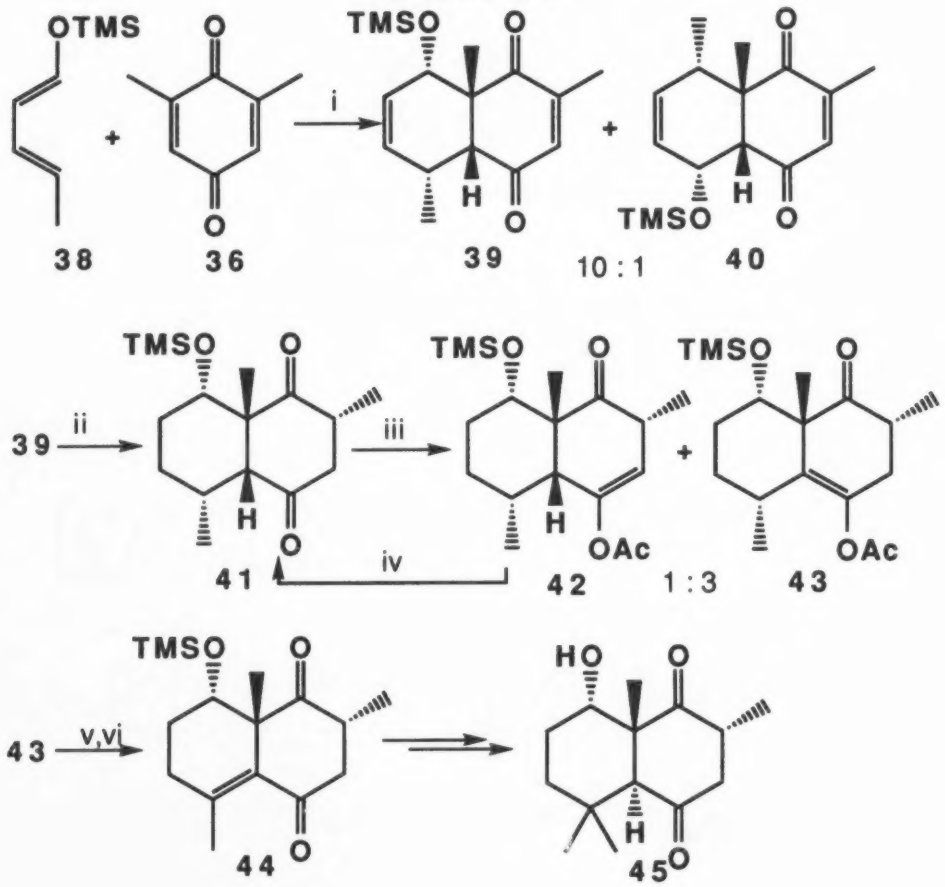
32 **33** **34**

Taking a similar approach and using a less hindered diene **38**, Sih *et al.* prepared **44** (Scheme 2-8).[31] They devised three ways to add the second methyl group to C-4, all utilizing methyl cuprates. However, no further report on this approach was found.

Scheme 2-7



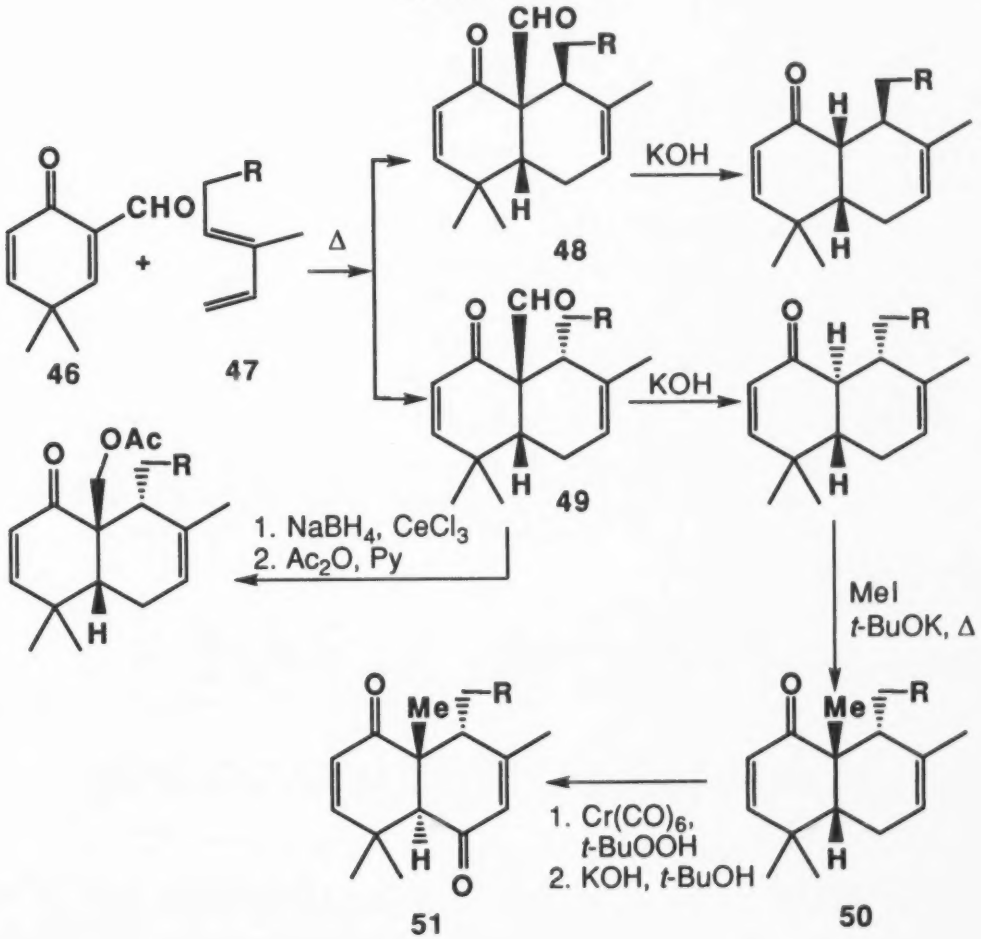
Scheme 2-8



i. PhMe, sealed tube, 120 °C, 65 hr, 50%; ii. H_2, Pd-C, EtOAc, 97%; iii. $H_2C{=}C(Me)OAc$, TsOH, 94%; iv. $H_3{}^+O$; v. $PhSeO_2CCF_3$; vi. H_2O_2, 57% for two steps.

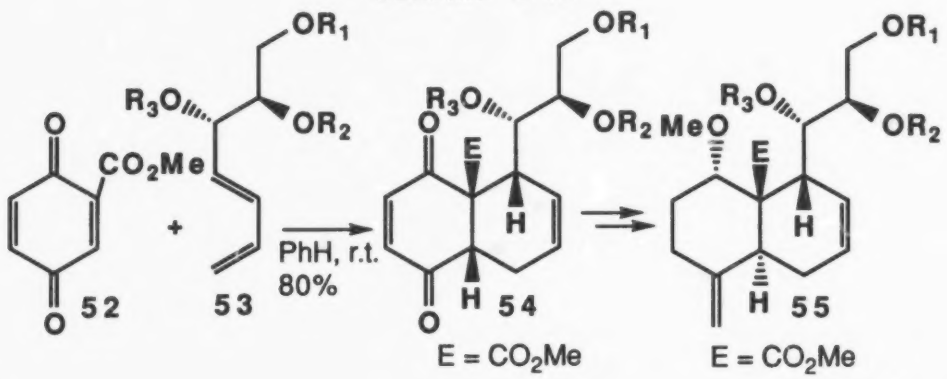
In 1993, Bhat *et al.* reported the use of a dienone-aldehyde **46** as the dienophile with 11 different kinds of dienes in their intermolecular approach to the A-B ring system (Scheme 2-9).[32] The major problem, besides the formation of mixtures of the *exo*- and *endo*-adducts, **48** and **49**, was the tendency to lose the formyl group upon contact with silica gel. Methylation with methyl iodide to re-install the angular carbon attached to C-10 was low yielding (5-45% yields). Further oxidation to introduce oxygenation at C-6 was also low yielding.

Scheme 2-9



Bhakuni and co-workers utilized the intermolecular Diels-Alder reaction of the optically active dienes **53** (R_1, R_2, R_3 = H, Ac, TMS, Me, THP and benzylidene) derived from D-glucose (Scheme 2-10). The reactive dienophile **52** was prepared *in situ* from the corresponding hydroquinone by oxidation with Ag_2O at room temperature.[33] The two keto groups in the adducts could be differentiated. After the carbonyl at C-1 was protected by forming a ketal group, or selectively reduced, the second one underwent a Wittig reaction to furnish an exocyclic double bond.

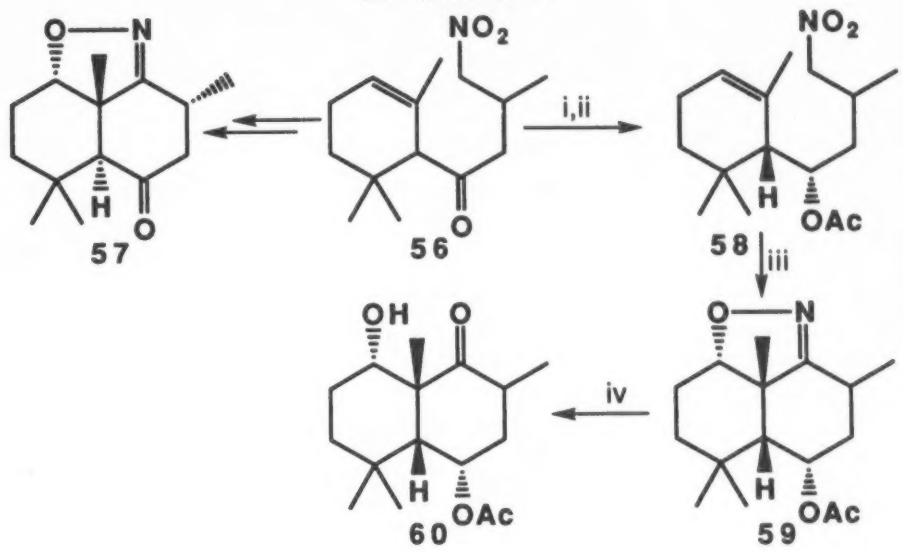
Scheme 2-10



In 1986, Barco, Pollini and co-workers took advantage of the intramolecular nitrile oxide cycloaddition (INOC) reaction to prepare **57** (Scheme 2-11), albeit in low yield (20%).[34] Later, they found a high yielding route to **60**, an intermediate which would eventually lead to forskolin. Compound **56** was derived from natural product α-damascone and nitromethane by Michael addition.[35]

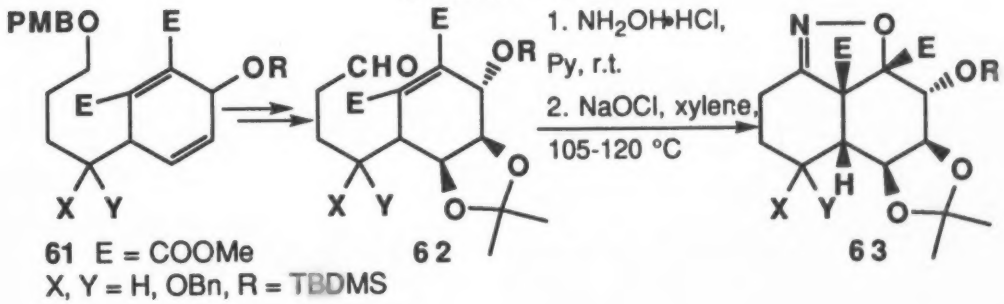
Kozikowski *et al.* demonstrated the feasibility of their INOC strategy in constructing highly oxygenated decalin derivatives like **63** (Scheme 2-12). Compound **61** was prepared by a Diels-Alder reaction of dimethyl acetylene-dicarboxylate.[36]

Scheme 2-11



i. $LiAlH_4$, $AlCl_3$, Et_2O; ii. Ac_2O, Py, r.t., 100%; iii. *m*-Cl-PhNCO, PhH, Et_3N, Δ, 48 hr, 85%; iv. H_2 / Ni (W-2), MeOH, H_2O, AcOH.

Scheme 2-12

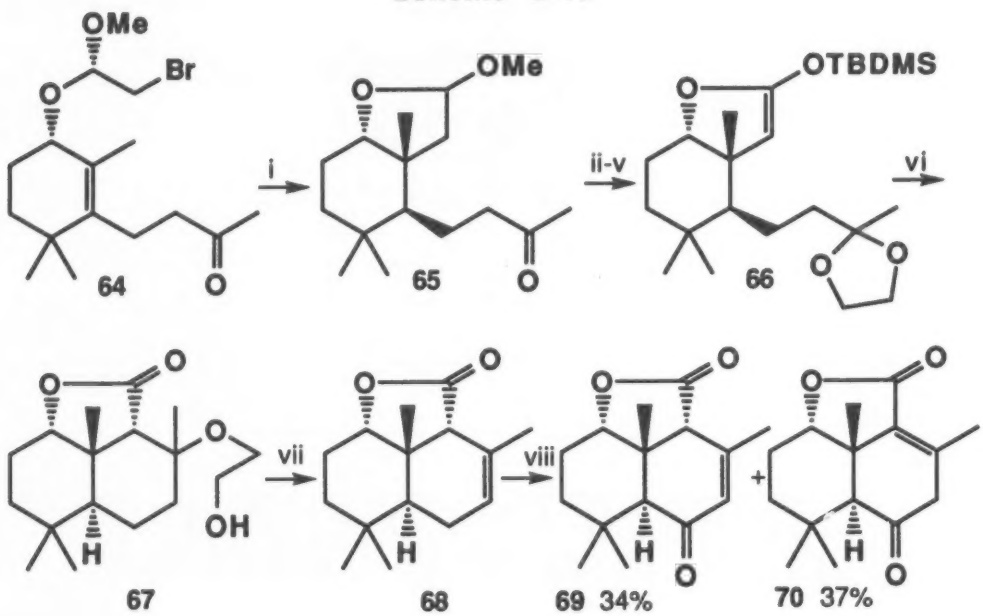


Pattenden and co-workers achieved a synthesis of the Ziegler intermediate **69** through radical cyclization of **64** in conjunction with Mukaiyama's version of aldol reaction and allylic oxidation (Scheme 2-13).[37]

Koft *et al.* found that the acetoacetate ester **71**, on treatment with cesium carbonate, underwent tandem Michael-aldol reactions followed by

deacetylation and double bond migration to give diene lactone **72**, an intermediate in Corey's scheme (Scheme 2-14).[38] Similarly, Li and Wu reported the synthesis of the tricyclic lactone **34** from the acetoacetate **73** by the Michael-aldol reaction sequences, giving lactone **34** and other products.[39] The yield for **34** was improved by Ruveda in a recent report.[40,41] Compound **34** would lead to **69** and **112** found in Ziegler's scheme.

Scheme 2-13

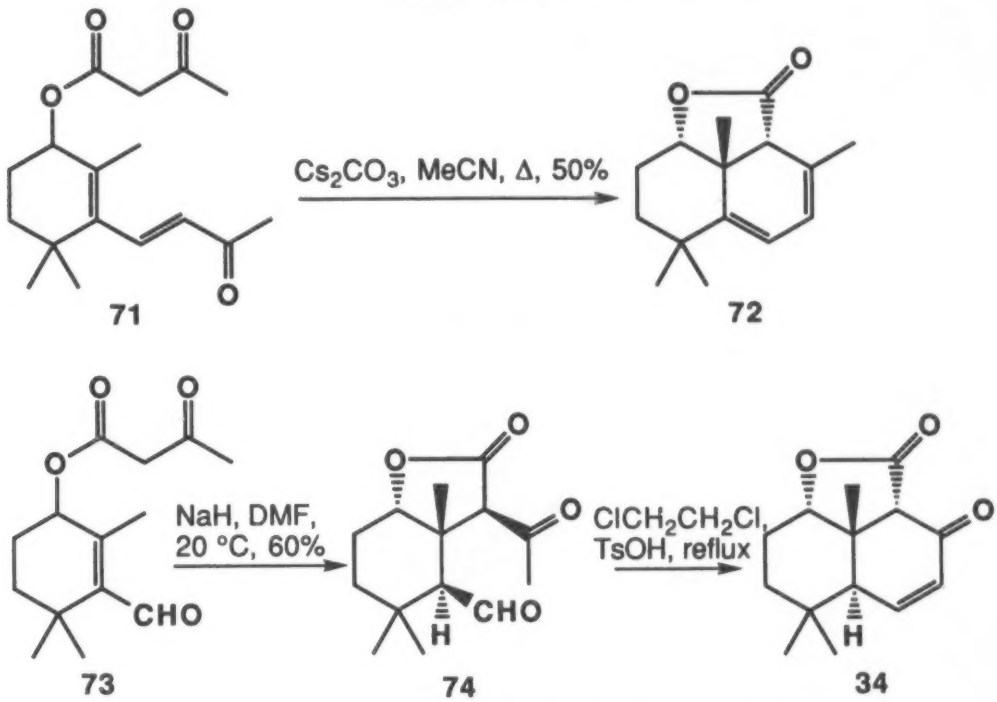


i. Vit. B_{12}, MeOH, $LiClO_4$, -1.8 v, r.t., 70%; ii. H_2CrO_4; iii. $HOCH_2CH_2OH$, TsOH; iv. LBTMSA; v. TBDMSCl, -70 °C, then 0 °C, 95%; vi. $TiCl_4$, CH_2Cl_2, -78 °C, 62%; vii. KOH, MeOH, Δ; viii. *t*-BuOOH, PDC, PhH, r.t.

By using electrocyclization which involved a series of 1,5- and 1,7-hydrogen migration, Cha *et al.* reported[42] the synthesis of bicyclic derivative **76** from **75**, which was readily available from α-ionone (Scheme 2-15). Compound **76** could be converted to **72** *via* the removal of the protecting group on the oxygen at C-1, oxidation and subsequent reduction to invert its

stereochemistry, and lactonization. Compound **69** was prepared from **72** in a few more steps. Thermolysis of the free hydroxy compound **77**, reported by Leclaire *et al.*, gave a mixture of two compounds, **72** and **78** (Scheme 2-15).[43]

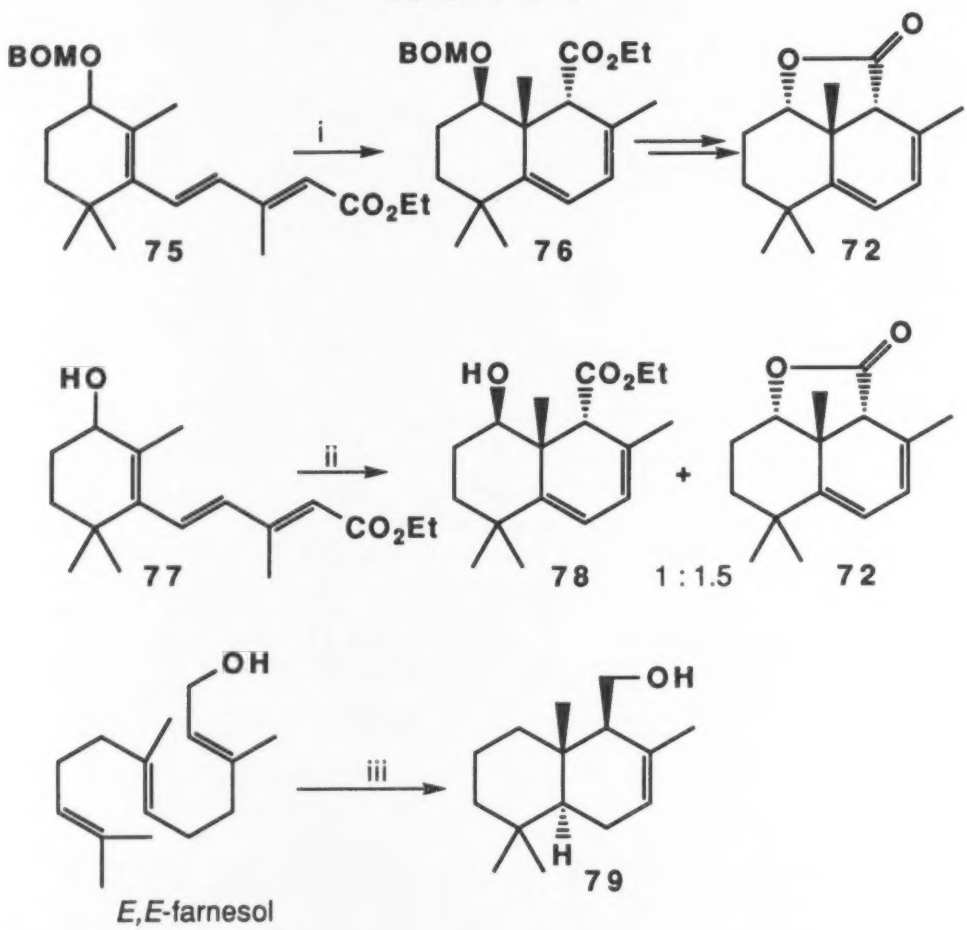
Scheme 2-14



71 72 73 74 34

A recent attempt to combine photochemical isomerization of the double bonds and thermal cyclization did not improve the yield or selectivity.[44] A more elegant approach toward the A-B ring synthesis was demonstrated in the cyclization of *E,E*-farnesol to yield the bicyclic compound **79** (Scheme 2-15).[45,46] This was also utilized by Welzel and co-workers in their efforts towards the synthesis of 1,9-dideoxyforskolin.[47] Similarly, this strategy was taken by Nicolaou to synthesize advanced intermediates of forskolin, as will be discussed later.[48]

Scheme 2-15



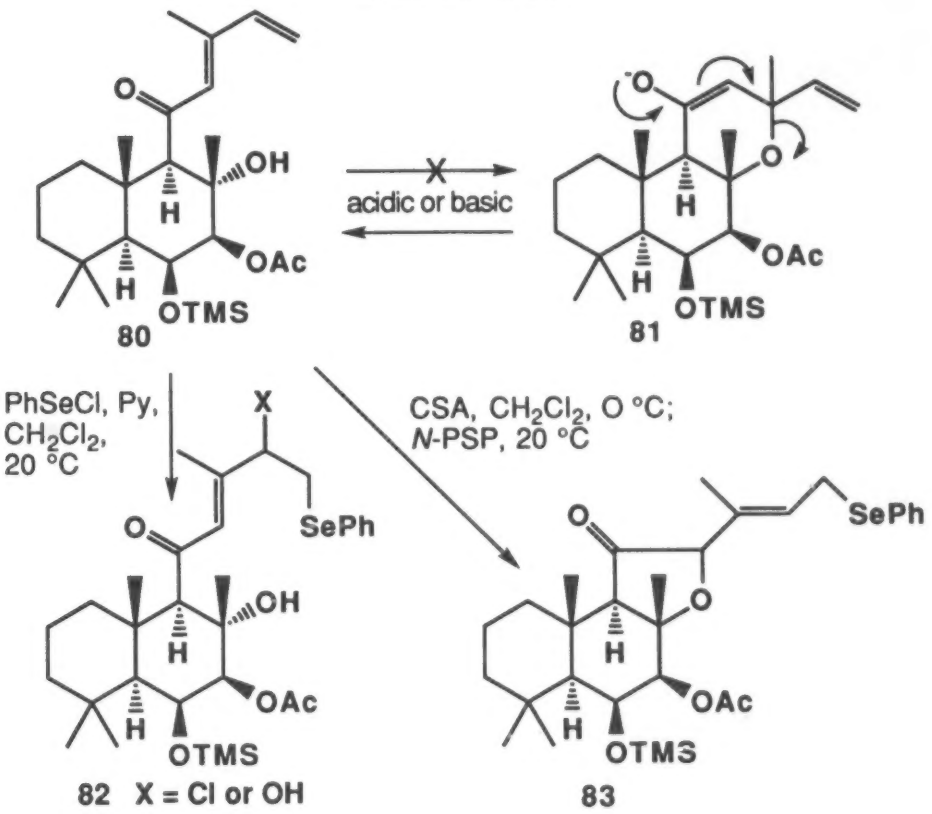
i. *N,N*-dimethylaniline, 240 °C or benzanthrone, *hv*, THF, DMF, 140 °C, 60-70%; ii. *N,N*-dimethylaniline, 245 °C, 6 hr, 65%; iii. FSO_3H.

Syntheses and elaboration of the C-ring

A simple look at the structure of forskolin might suggest that the addition of the C-8 hydroxy group to a dienone under acidic or basic conditions to furnish the C-ring. However, it was found by Welzel *et al.* that with a derivative of 1,9-dideoxyforskolin **2**, the reverse happened due to the strain in the newly

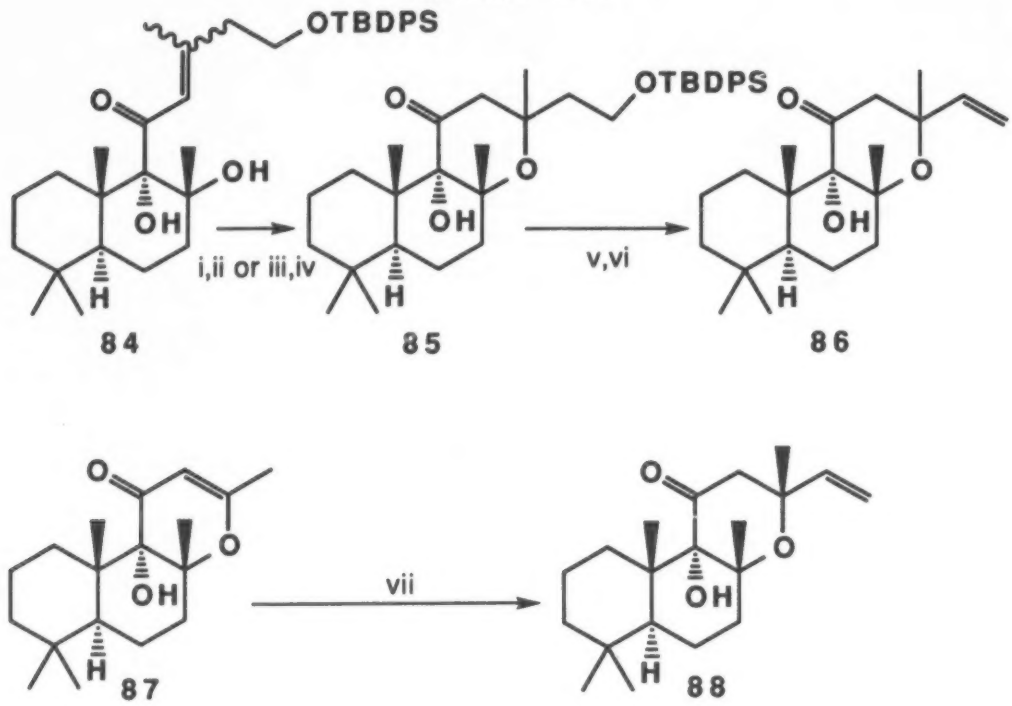
formed ring-C and the loss of conjugation (Scheme 2-16).[49] Attempts to trap the enol at C-12 with PhSeCl or *N*-phenylselenophthalimide (*N*-PSP) also failed.

Scheme 2-16



Soon thereafter, Ikegami reported several solutions to the problems of the C-ring elaboration (Scheme 2-17).[50] The first one was the addition of the 8-hydroxyl group to an α,β-unsaturated ketone, assisted by phenylselenenyl chloride or mercuric trifluoroacetate. The C_{14}-C_{15} double bond was generated afterward, by freeing the hydroxy group at C_{15} and applying Grieco's methodology[51] of dehydration. The second one was the addition of a higher order vinyl cuprate.[52,53]

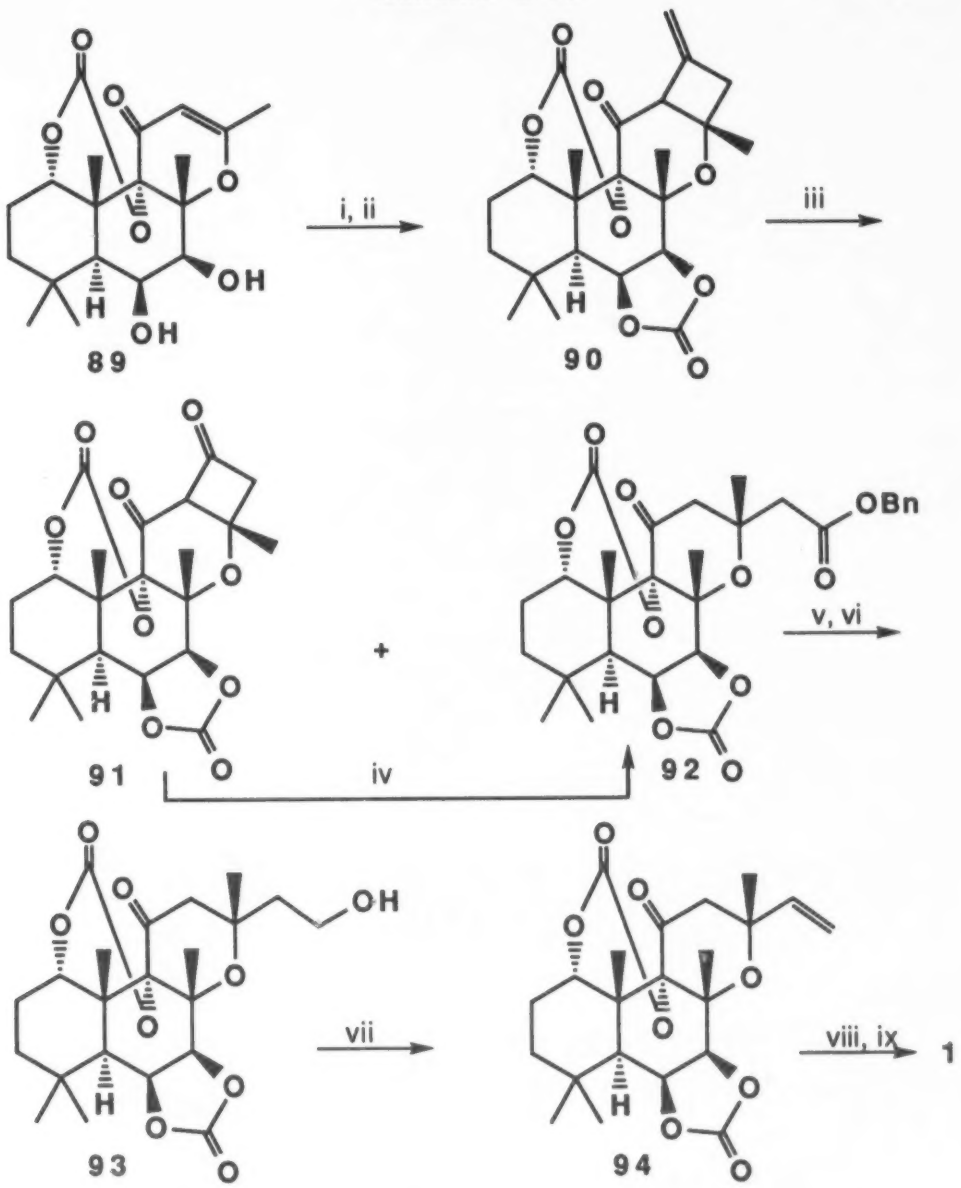
Scheme 2-17



i. PhSeCl, CH_2Cl_2, -78 °C to -40 °C; ii. Raney-Ni (W-2), MeOH, 77%; iii. $Hg(O_2CCF_3)_2$, CH_2Cl_2, -78 °C; iv. LiI, Et_2O, Et_3N, 75%; v. H_3^+O, THF, 94%; vi. *o*-$O_2NC_6H_4SeCN$, Bu_3P, THF, H_2O_2, CH_2Cl_2, 74%; vii. $(CH_2{=}CH)_2Cu(CN)Li_2$, Et_2O, 0 °C, 10 min, 80%.

By using a photochemical reaction as the key step, Ziegler *et al.* developed a completely different approach to add the C-ring vinyl group of forskolin (Scheme 2-18).[54] Irradiation of **89** in the presence of allene gave a single product in excellent yield. After protecting the diol as a carbonate, the exocyclic double bond was cleaved to give a diketone **91** as the major product and a ring-opening product **92**. The former was converted to the latter in 60% yield which afforded **93** upon hydrogenolysis and reduction. Grieco's dehydration, deprotection and final acetylation concluded the total synthesis of forskolin **1**.

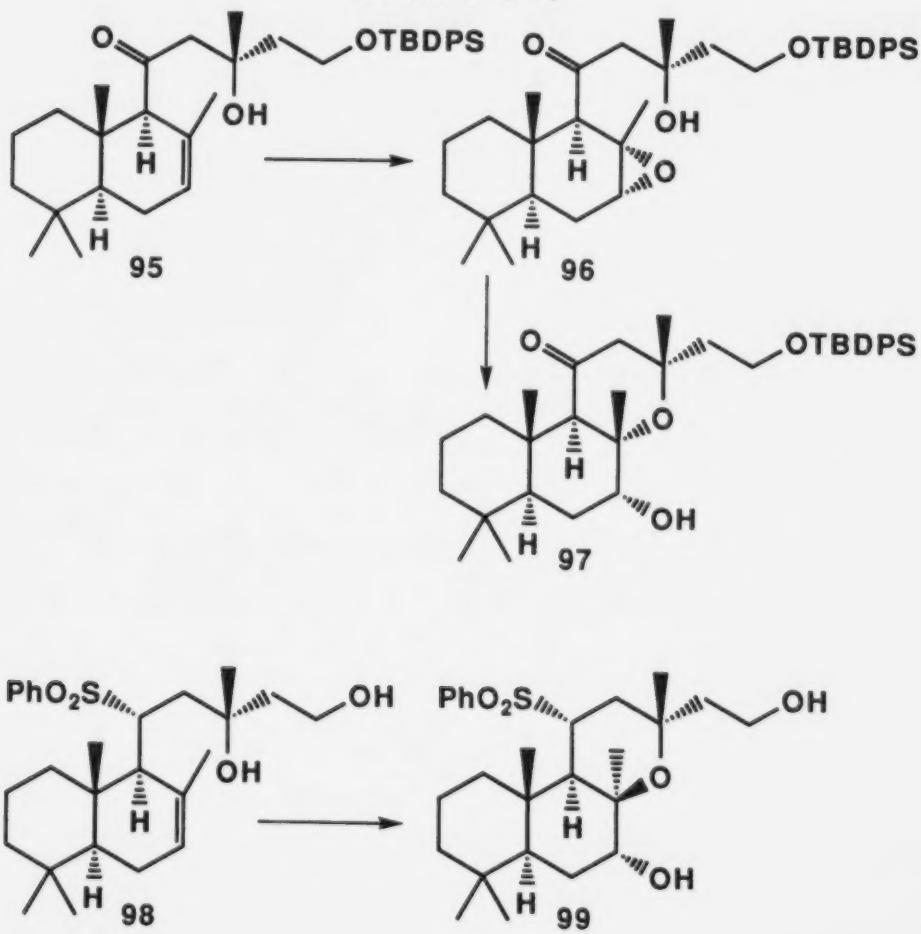
Scheme 2-18



i. $H_2C{=}C{=}CH_2$, *hv*, Et_2O, THF, -55 °C, 96%; ii. Cl_2CO, CH_2Cl_2, Py, DMAP, 0 °C to 25 °C, 97%; iii. O_3, CH_2Cl_2, BnOH, Me_2S, -78 °C; iv. BnOH, CH_2Cl_2, Py, DMAP, 25 °C, 60%; v. H_2, Pd-C, 1 atm, EtOAc, 25 °C; vi. BH_3•THF, 25 °C, 41% (two steps); vii. *o*-$O_2NC_6H_4SeCN$, Bu_3P, 25 °C, H_2O_2, THF, 25 °C; ix. Ac_2O, Py, 25 °C, 88%.

Welzel *et al.* took an approach opposite to Ikegami's. They established the hydroxy group at C-13 first and used it to attack the B-ring at C-8 (Scheme 2-19).[47] Trimethylsilyl triflate-mediated cyclization of **96** gave a single product, **97**, whose structure and stereochemistry was established by NOE and X-ray analysis. It turned out that this was the desired one. Direct addition of the hydroxy group to the double bond, assisted by *N*-PSP, was also attempted with a similar compound **98**. In this case, compound **99** with the wrong configuration at C-8 was produced. Mercury(II) trifluoroacetate catalyzed cyclization gave the same configuration at C-8.

Scheme 2-19

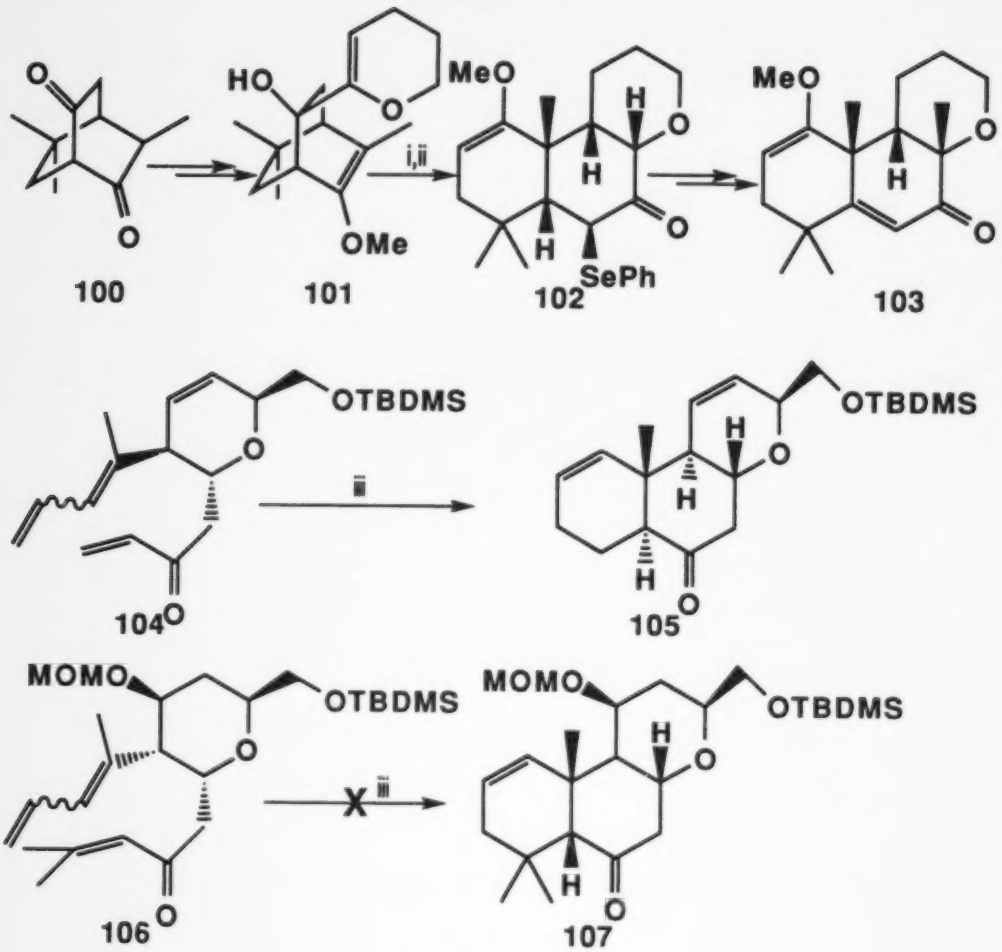


Approaches towards the A-B-C ring system of forskolin

There were two unique approaches, whereby the B- and C-rings were formed at the same time. Paquette *et al.* incorporated an anionic oxy-Cope rearrangement as the key step in building up the tricyclic system (Scheme 2-20).[55] Compound **100** was prepared from 2,4,4-trimethylcyclohexenone in 3 steps in 75% yield. By selectively protecting one ketone, the other one was reacted with 2-lithiodihydropyran to form **101**. Anionic oxy-Cope rearrangement followed by trapping the enolate with PhSeCl afforded **102** in 79% yield. Oxidative elimination and subsequent methylation gave **103**. In order to synthesize more advanced intermediates, Paquette *et al.* prepared several highly functionalized 3,4-dihydro-2*H*-pyrones and pyrans. However, compounds like **102** could not be obtained in decent yield, due to problems associated with the metallation of the pyrones or pyrans, their additions to the ketone or the rearrangements.[56]

Hanna and co-workers prepared the optically active compounds **104** and **106** from tri-*O*-acetylgalactal (Scheme 2-20).[57] Intramolecular Diels-Alder cyclization of **104** under BF_3 catalysis gave a moderate yield of the adduct **105**. However, when they tried to incorporate the *gem*-dimethyl group and a slightly different protecting group into the precusor **106**, no adduct was obtained under either thermal conditions or Lewis acid catalysis, due to the steric interactions in the transition state.[44]

Scheme 2-20

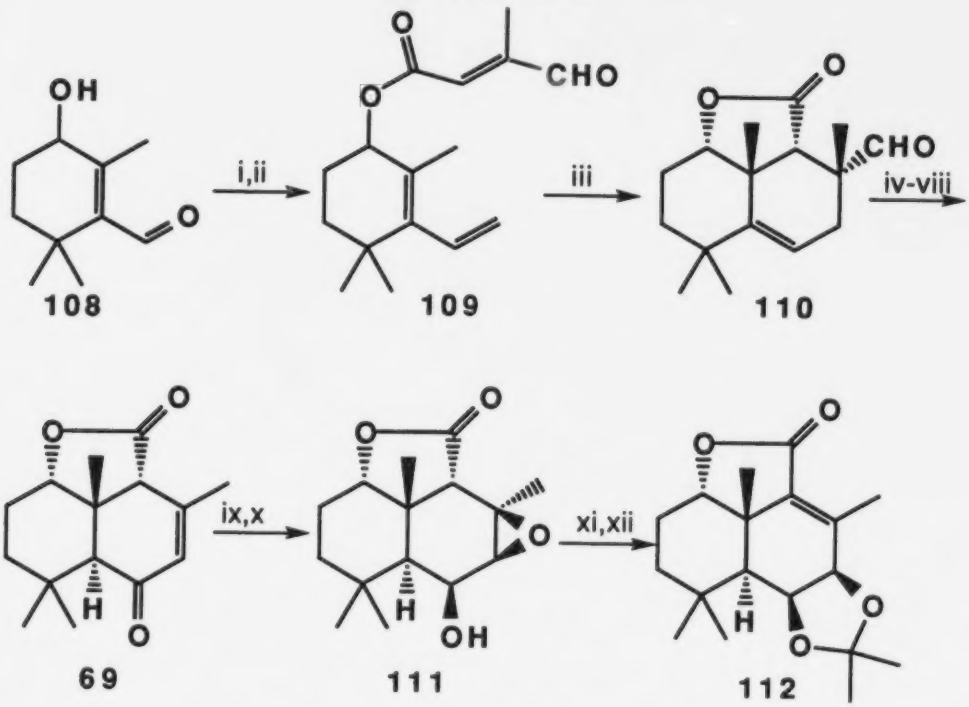


i. KH, THF, 18-crown-6, 70 °C; ii. PhSeCl, 79%; iii. BF_3, CH_2Cl_2, 0 °C, 50%.

Total syntheses of forskolin

In 1985, Ziegler and co-workers first prepared the tricyclic lactone **112** (Scheme 2-21).[58] Intramolecular Diels-Alder reaction put all the carbons of the A-B ring in place. Further elaboration of functional groups by hydroboration, oxidation, epimerization and oxidative elimination with lead tetraacetate led to

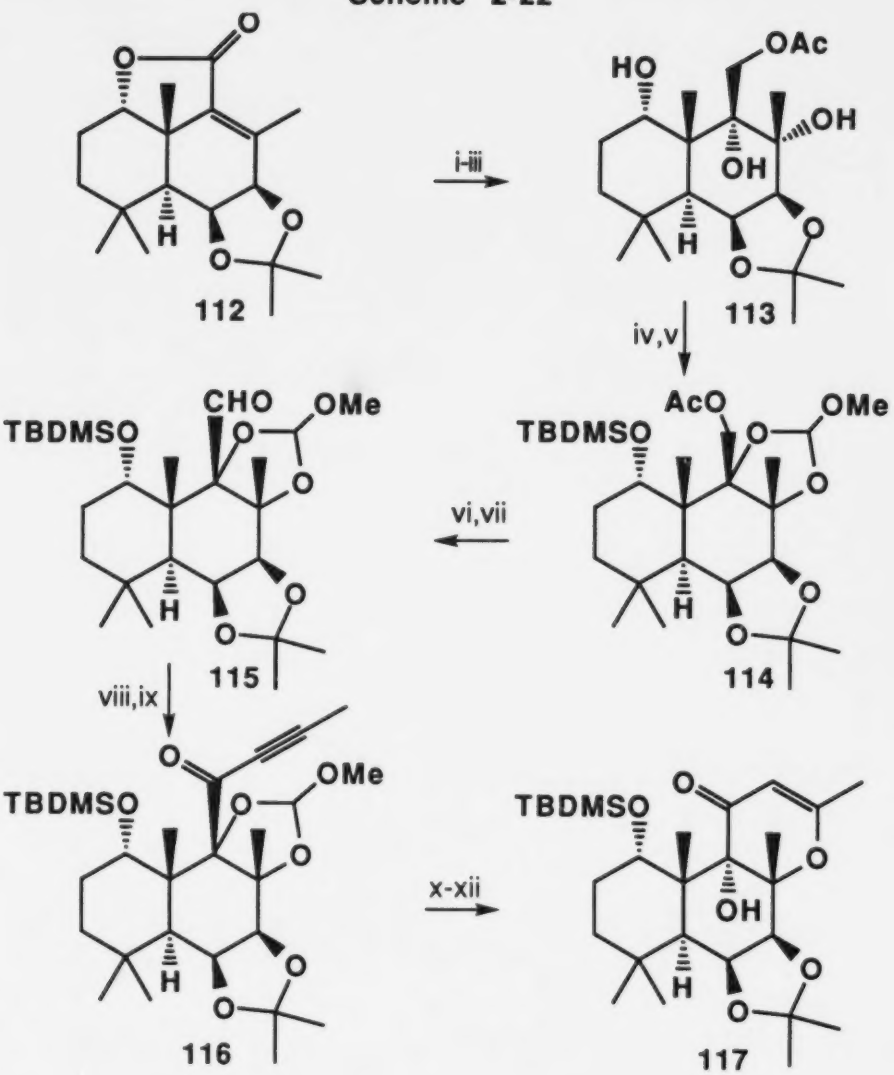
Scheme 2-21



i. $Ph_3P{=}CH_2$, THF; ii. (*E*)-3-methyl-4-oxo-2-butenoic acid, DCC, DMAP; iii. PhH, 120 °C; iv. $BH_3{\bullet}THF$, 0 °C; NaOOH; v. Jones reagent; vi. CH_3OK, CH_3OH; vii. $Pb(OAc)_4$, Py; viii. $LiBH_4$, Li_2CO_3, EtOH; ix. $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; x. $LiNEt_2$, THF; xi. 2,2-dimethoxypropane, *p*-TsOH.

lactone **69**. Reduction of the enone to the allylic alcohol, subsequent Sharpless oxidation followed by epoxide ring opening with $LiNEt_2$ and protection of the vicinal diol gave **112**. In a subsequent publication,[18] these authors reported conversion of lactone **112** to tricyclic pyranone **117** (Scheme 2-22). They elaborated the C-ring by a 1,4-addition of methoxide anion to acetylenic ketone **116**, prepared from **112** *via* intermediates **113**, **114** and **115**. Acid-catalyzed cyclization provided **117**. Linkage of **117** with **89** was achieved by removal of the silyl group, protecting the 1,9-diol as a carbonate and removal of the acetonide group (Scheme 2-23). Compound **89** was also

Scheme 2-22

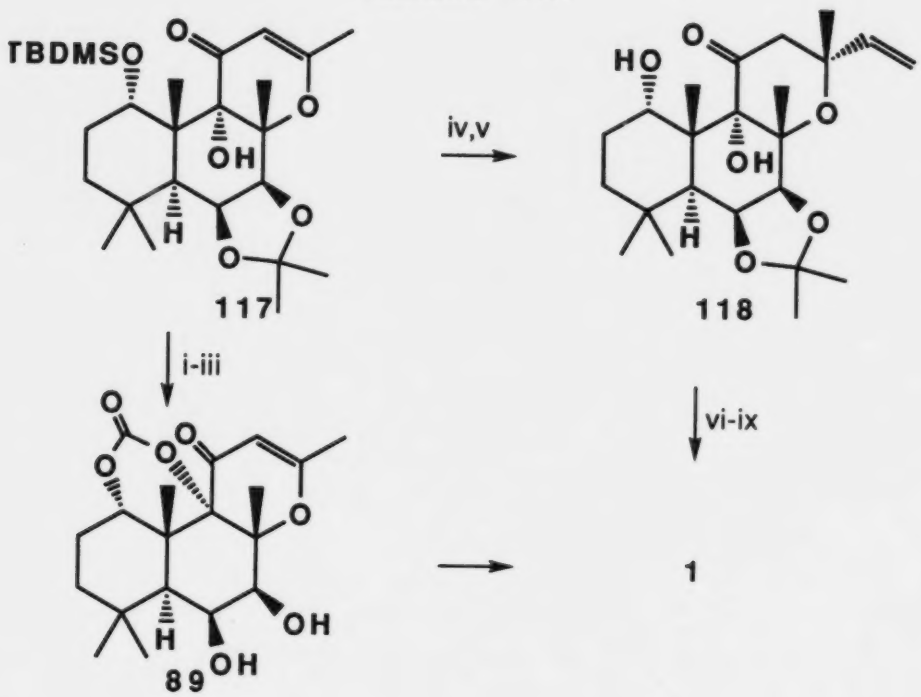


i. $LiAlH_4$, Et_2O; ii. *N*-acetylimidazole, DBU, PhH; iii. OsO_4, Py; iv. TBDMSOTf, 2,6-lutidine, CH_2Cl_2; v. neat $CH(OMe)_3$, *p*-TsOH; vi. KOH, MeOH, THF; vii. CrO_3•2Py, CH_2Cl_2; viii. 1-lithiopropyne, THF; ix. CrO_3•2Py, CH_2Cl_2; x. 3N HCl, THF (1:25), then MeOH-NH_3; xi. KOH, MeOH; xii.*p*-TsOH, PhH.

obtained by degradation of natural forskolin. Its conversion to forskolin was completed by Ziegler *et al.* in 1987, as shown in Scheme 2-18, *via* photocyclization with allene and subsequent modifications.[54] This formally

completed the first total synthesis of forskolin. One year later, Ziegler and co-workers were able to add a vinyl anion to the α-face of their intermediate **117**.[53] Further deprotection and acetylation also gave forskolin.

Scheme 2-23



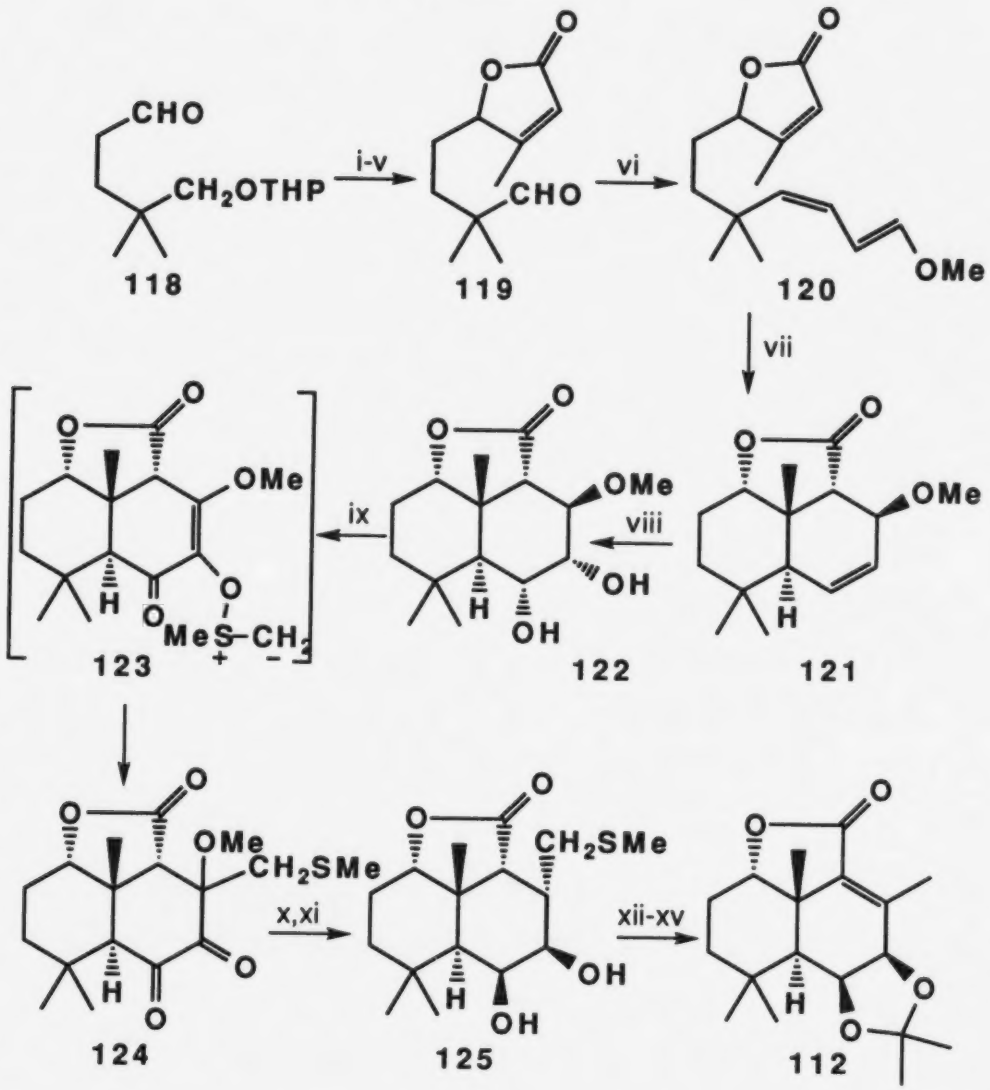
i. $(n\text{-Bu})_4NF$, THF; ii. $COCl_2$, Py, CH_2Cl_2; iii. 3 N HCl-THF (1:5); iv. $(CH_2{=}CH)_2Cu(CN)Li_2$, $BF_3{\bullet}Et_2O$; v. $(n\text{-Bu})_4NF$, THF; vi. $COCl_2$, Py, CH_2Cl_2 ; vii. 3 N HCl, dioxane; viii. 2 N NaOH, MeOH; ix. Ac_2O, Py, 0 °C.

The second total synthesis of forskolin was achieved by Ikegami *et al.* in 1988.[19] They took an intramolecular Diels-Alder approach to build the A- and B-rings in one step, by cyclization of lactone **120** (Scheme 2-24). Osmium tetraoxide oxidation followed by Parikh-modified Moffat oxidation gave diketone **124**, with a methylthiomethyl at C-8. $LiAlH_4$ reduction of the diketone, MCPBA

oxidation of the sulfide into sulfoxide, subsequent thermolysis and migration of the double bond gave **112**, the intermediate as appeared in Ziegler's scheme. Intermediate **112** was then transformed to forskolin by a sequence similar to that used by Ziegler *et al.*. The formation and elaboration of the C-ring involved the phenylselenenyl chloride assisted cyclization and Raney-Ni removal of the phenylselenenyl group, deprotection of the hydroxy group and Grieco's dehydration (Scheme 2-25).

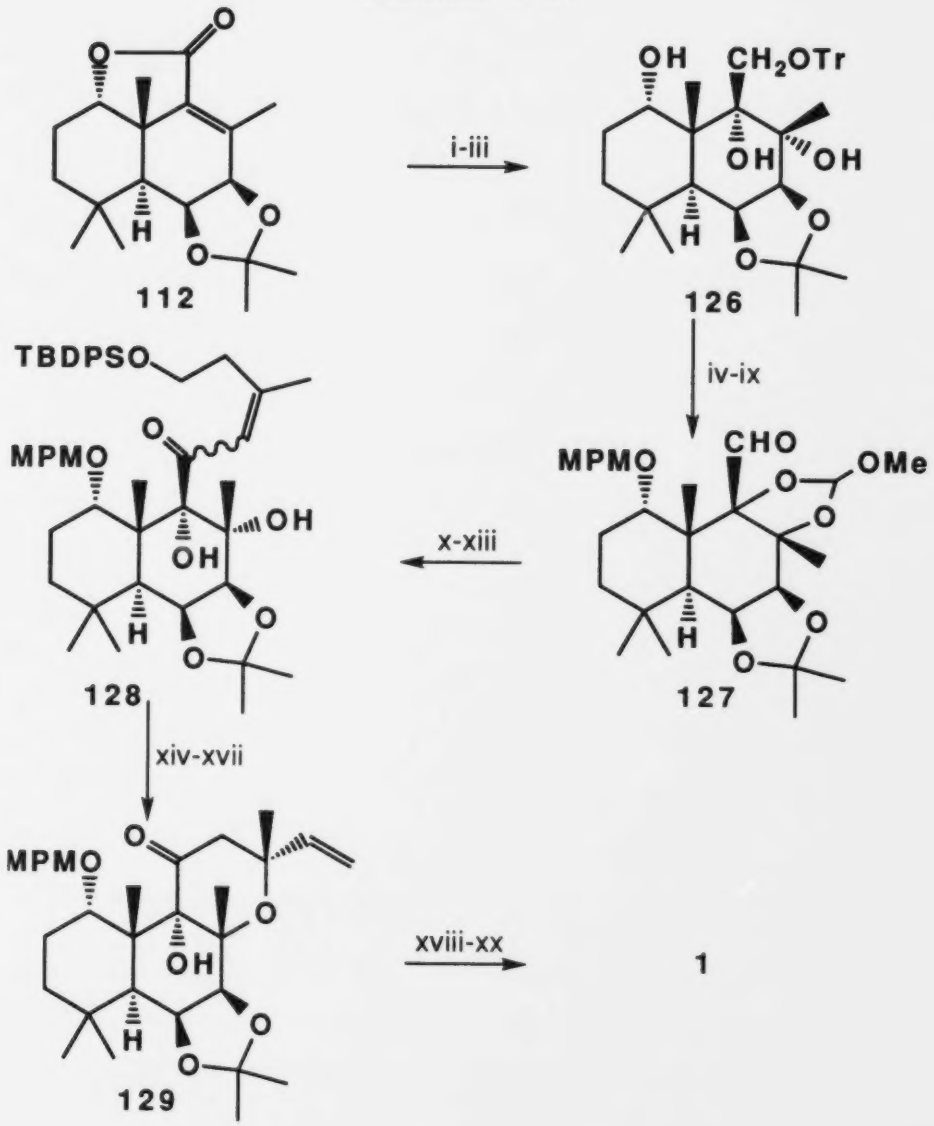
The third total synthesis was achieved by Corey and co-workers in 1988.[20] Intramolecular Diels-Alder reaction of the acetylenic ester, substitution of the tosyl group with a methyl group and double bond migration provided the diene lactone **130** (Scheme 2-26), which was also prepared in Koft, Cha and Leclaire's laboratories, as shown in Schemes 2-14 and 2-15. Photochemical cycloaddition of singlet oxygen to **130** gave endoperoxide **131**, which, upon reduction and benzoylation, provided **132**. 1,3-Keto transposition, reduction and double bond migration gave the same intermediate **112**, as appeared in Ziegler's and Ikegami's schemes. Direct ethynylation of **112** and subsequent protection of the C-1 hydroxy group with dimethylcarbamoyl chloride afforded **134** (Scheme 2-27). Conjugate addition of a hydroxy group to ynone **134**, resilylation of the primary alcohol and acetylation yielded β-acetoxydienone. On treatment with singlet oxygen, the β-acetoxydienone yielded endoperoxide **136**, apparently through the intermediacy of **135**. Sequential treatment of **136** with sodium ethoxide in the presence of tributylphosphine, acetic acid-acetic anhydride and methyl copper-tributylphosphine complex in the presence of boron trifluoride etherate gave rise to compound **137**. The vinyl group was introduced using a reaction sequence similar to that described by Ikegami and co-workers and the synthesis of forskolin was completed after a few more steps of deprotection and acetylation.

Scheme 2-24



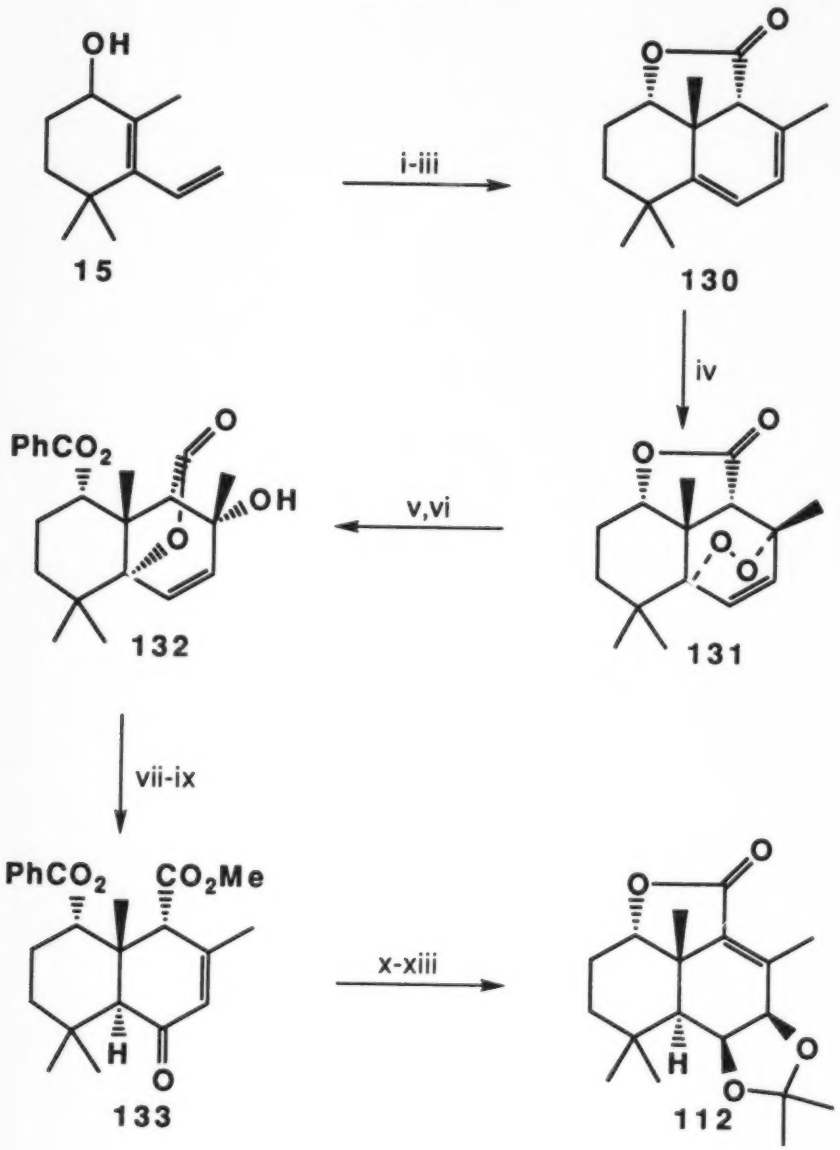
i. LiC≡CCO$_2$Me, THF, -78 °C; ii. dihydropyran, *p*-TsOH, CH_2Cl_2; iii. Me_2CuLi, THF, -70 °C; iv. *p*-TsOH, MeOH; v. PCC, CH_2Cl_2; vi. MeOCH=CHCH$_2$P$^+$Ph$_3$Br$^-$, *n*-BuLi, -78 °C, THF; vii. PhSH, PhMe, sealed tube, 220 °C; viii. OsO_4, Me_3N-O, Py, *t*-BuOH - H_2O, reflux; ix. SO_3•Py, Et_3N, DMSO; x. NaTeH, EtOH; xi. *t*-BuNH$_2$•BH$_3$, MeOH; xii. $Me_2C(OMe)_2$, *p*-TsOH, PhH; xiii. MCPBA, CH_2Cl_2; xiv. $CaCO_3$, PhMe, reflux; xv. LiOMe, THF.

Scheme 2-25



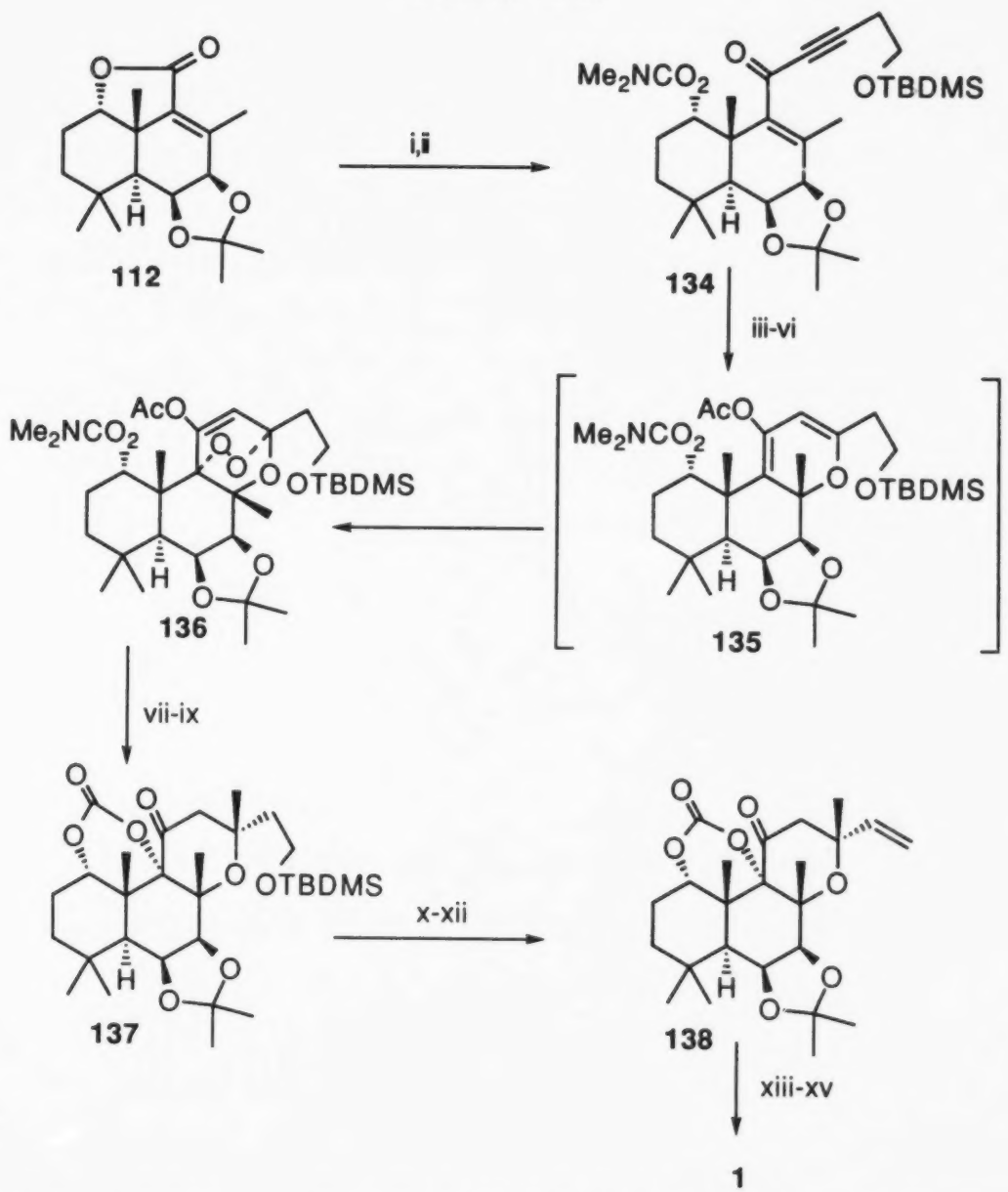
i. $LiAlH_4$, Et_2O; ii. TrCl, DMAP, 1,2-dichloroethane; iii. OsO_4, Py, then H_2S, $CHCl_3$-dioxane; iv. NaH, *p*-$MeOC_6H_4CH_2Cl$, HMPA; v. *p*-TsOH, $CHCl_3$-MeOH; vi. Ac_2O, Py; vii. $HC(OMe)_3$, *p*-TsOH; viii. $LiAlH_4$, Et_2O; ix. SO_3•Py, DMSO; x. $LiC{\equiv}CCH_2OTBDPS$, -78 °C, THF; xi. MnO_2, PhH; xii. Me_2CuLi, Et_2O, -78 °C; xiii. 3 N HCl-THF, then KOH-MeOH-THF; xiv. PhSeCl, CH_2Cl_2, then Ra-Ni (W-2), EtOH; xv. (*n*-Bu)$_4$NF, THF; xvi. *o*-$O_2NC_6H_4SeCN$, (*n*-Bu)$_3$P, THF; xvii. 30% H_2O_2, CH_2Cl_2; xviii. DDQ, CH_2Cl_2-H_2O, then K_2CO_3, MeOH; xix. 10% aq $HClO_4$-THF; xx. Ac_2O, Py, 0 °C.

Scheme 2-26



i. TsC≡CCO$_2$H, CHCl$_3$; ii. Me$_2$CuLi, BF$_3$•Et$_2$O; iii. DBN; iv. O$_2$, *hv*, CHCl$_3$, methylene blue; v. Al / Hg, THF, H$_2$O; vi. (PhCO)$_2$O, DMAP, ClCH$_2$CH$_2$Cl; vii. PCC, CH$_2$Cl$_2$; viii. Al / Hg, THF, H$_2$O; ix. CH$_2$N$_2$, Et$_2$O; x. DIBAL, PhMe; xi. Mo(CO)$_6$, *t*-BuOOH; xii. KOH, MeOH; xiii. 2,2-dimethoxypropane, *p*-TsOH.

Scheme 2-27

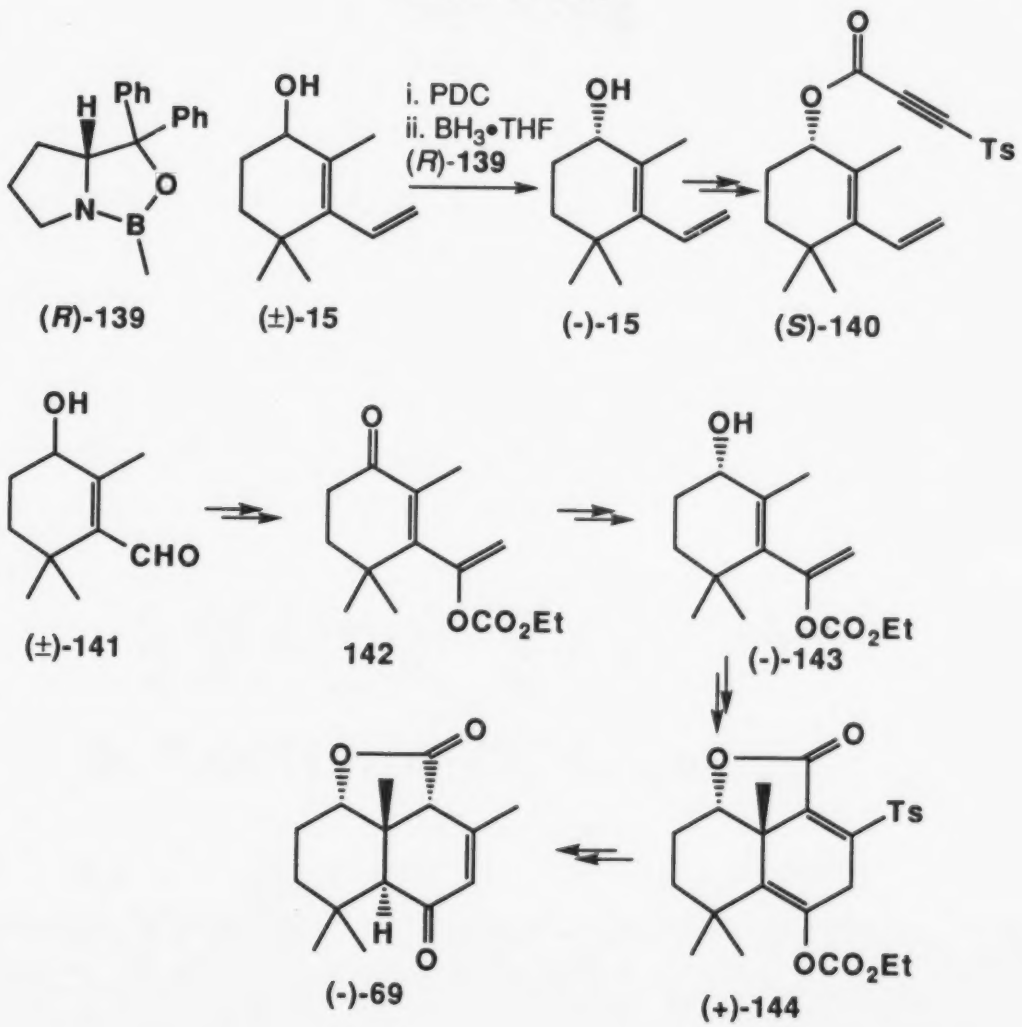


i. LiC≡C$(CH_2)_2$OTBDMS, THF; ii. Me_2NCOCl, 2,6-lutidine, AgOTf, CH_2Cl_2; iii. $(HOCH_2)_2$, K_2CO_3, THF; $(CO_2H)_2$, H_2O; iv. TBDMSCl, imidazole, DMF; v. TlOEt, r.t., AcCl; vi. O_2, *hv*, $CHCl_3$, 0 °C, methylene blue; vii. NaOEt, Bu_3P, EtOH; viii. HOAc, Ac_2O, 100 °C; ix. MeCu•PBu_3, BF_3•OEt_2, Et_2O; x. HF, MeCN, H_2O; xi. *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF; xii. H_2O_2, THF, r.t.; xiii. $H_2NCONHNH_2$, HOAc, H_2O, 70 °C; xiv. LiOH, THF-H_2O-*i*-PrOH, r.t.; xv. Ac_2O, Py, 0 °C.

Enantioselective syntheses of key intermediates

So far, three sequences based on enantioselective reduction were reported on the synthesis of optically pure intermediates used in the total synthesis of forskolin. Another three, based on chemical or enzymatical resolution of enantiomers were also developed. All of the reductions involved the use of the chiral-oxazaborolidine (**139**)-catalyzed borane reduction of achiral ketones, developed by Corey, Bakshi and Shibata (Scheme 2-28).[59]

Scheme 2-28



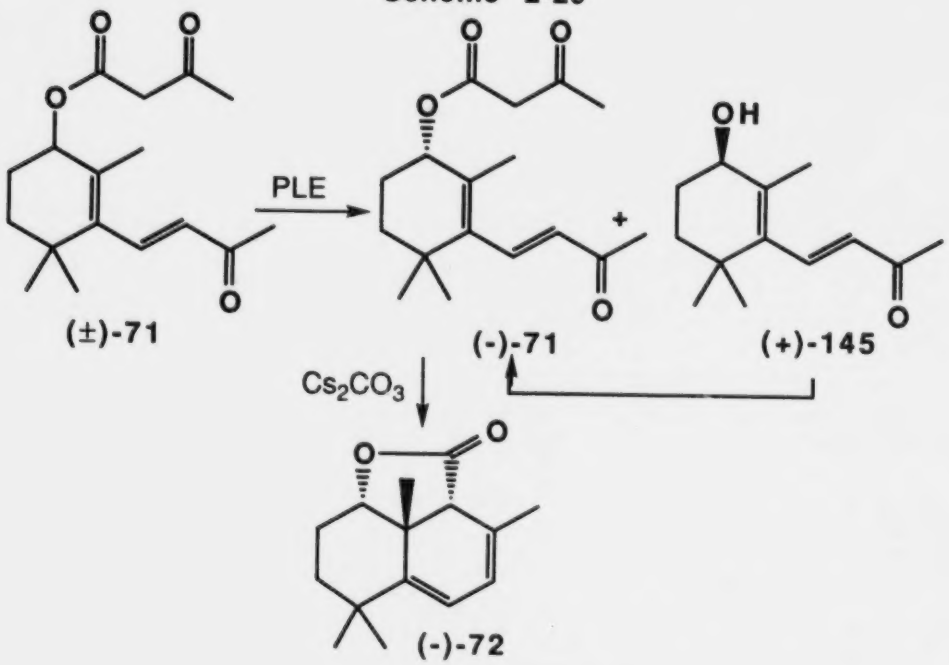
Corey *et al.* first reported[60] the preparation of ()-**15** in excellent yield and optical purity by the oxidation of (±)-**15** and subsequent reduction with BH_3 and (*R*)-**139**. Compound ()-**15** was incorporated into their total synthesis in essentially the same way. Recently, Kanematsu *et al.* also reported the use of ()-**15**, prepared in the same manner, in their synthesis of Ziegler intermediate **69**.[61] In a subsequent publication, Corey and co-workers reported a new route to the Ziegler intermediate **69** in optically pure form.[62] To overcome the difficulties of introducing oxygen at C-6 in the decalin system in the later stage, they installed an ester group in the dienone **142**. Reduction of the ketone group with BH_3 and (*R*)-**139** gave (-)-**143**, which was transformed into (+)-**144** and Ziegler intermediate (-)-**69**.

Lallemand *et al.* started with racemic **71** and used pig liver esterase (PLE) to selectively hydrolyze one enantiomer (Scheme 2-29).[63] The remaining ester, (-)-**71**, had the desired stereochemistry at C-1 and was transformed into (-)-**72** in 99% *ee*. The free alcohol, (+)-**145**, after Mitsunobo inversion of the configuration and acylation, provided the desired ester (-)-**71**.

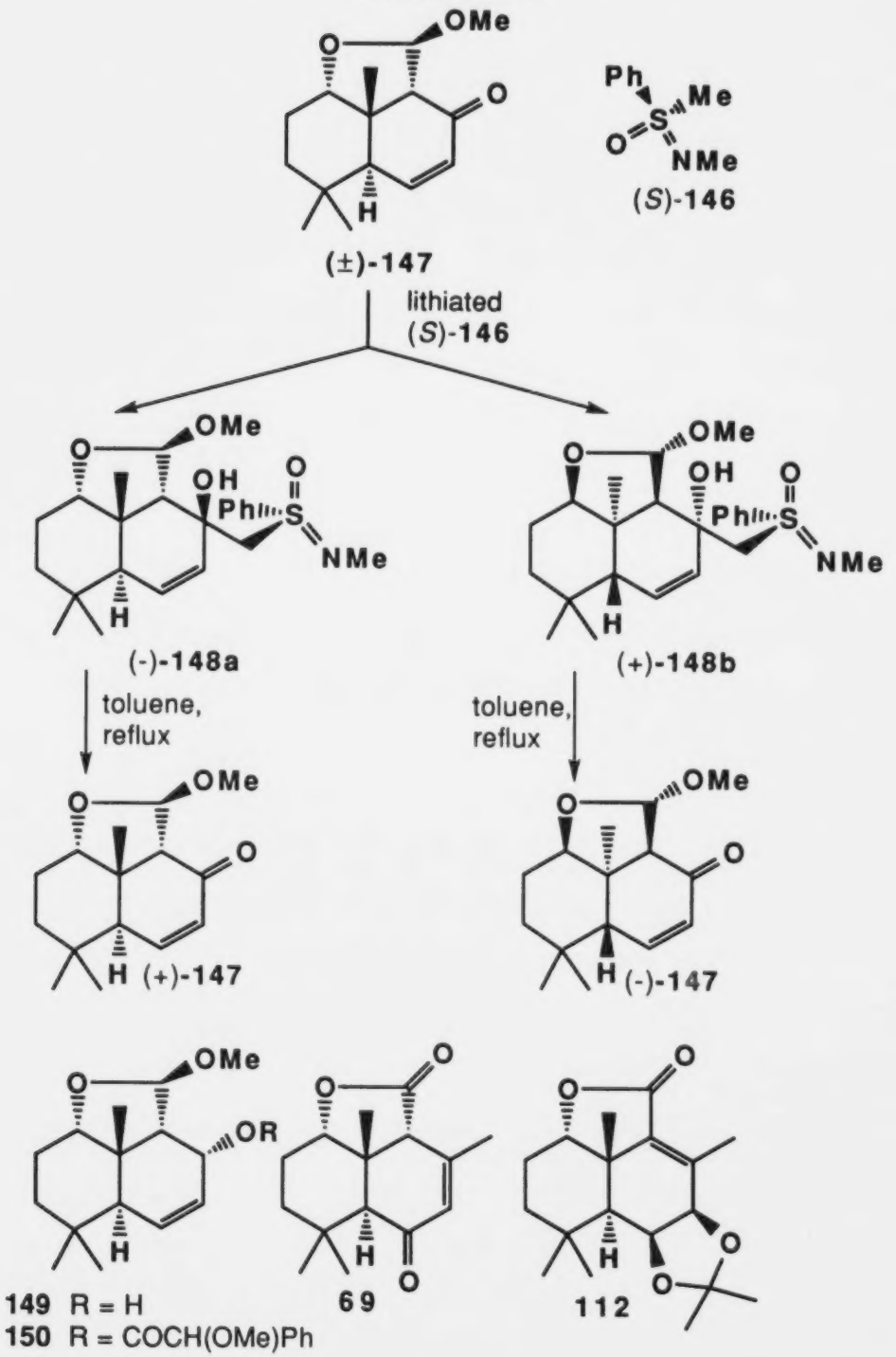
Ruveda *et al.* applied the Johnson sulfoximine resolution protocol to the resolution of (±)-**147** (Scheme 2-30).[64] Nucleophilic addition of the lithiated (*S*)-**146** to **147** afforded a chromatographically separable mixture of two diastereomers, (+)-**148b** and (-)-**148a**. To complete the resolution, each diastereomer was subjected to thermolysis in refluxing toluene to afford (+)- and (-)-**147**. Compound **147** was transformed into optically pure **69** in a few steps. In another effort to prepare enantiomerically pure intermediates, the same author resolved a racemic mixture of allylic alcohol **149** by esterification with (*R*)-(-)-*O*-methylmandelic acid.[65] The diasteromeric esters were separated and hydrolyzed to gave the enantiomerically pure allylic alcohols. The

stereochemically correct compound **149** was transformed into Ziegler intermediate **112**.

Scheme 2-29



Scheme 2-30

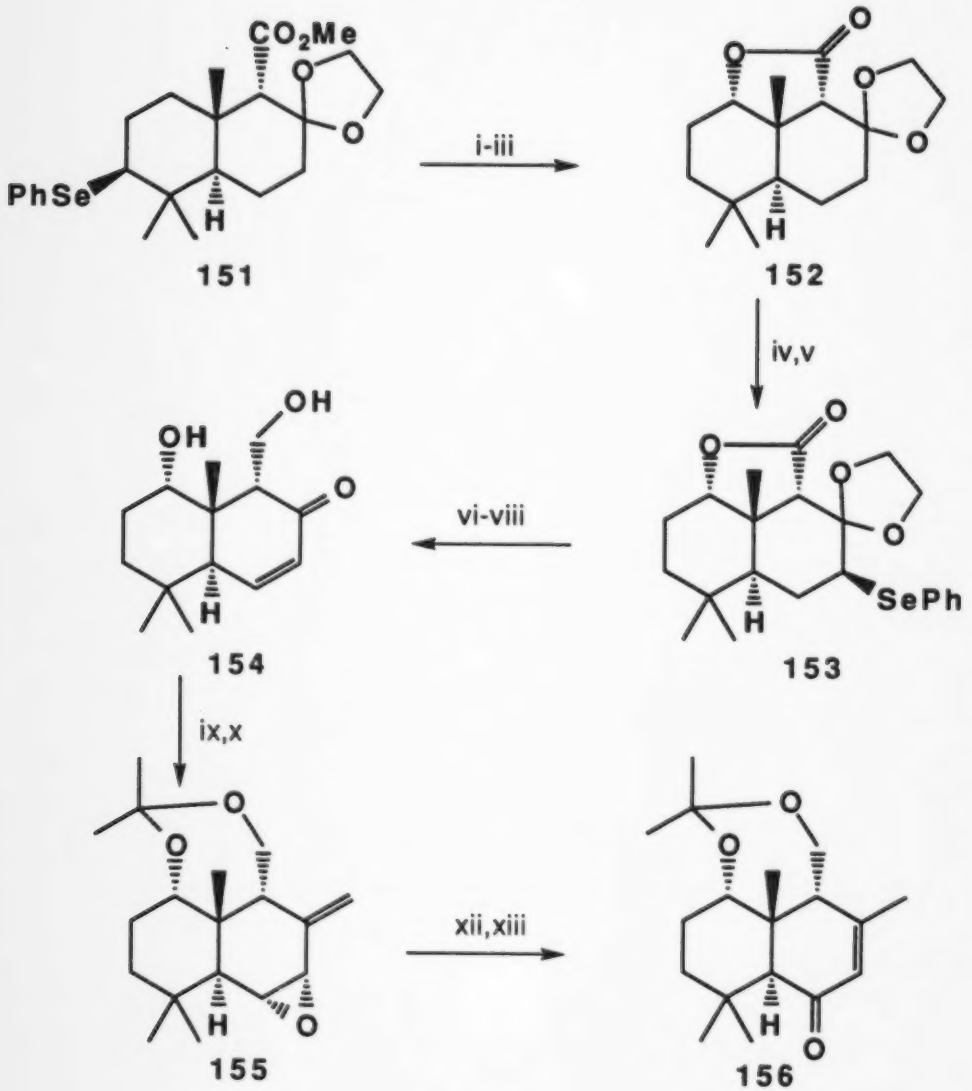

OMe
O
O
H
(±)-147
Ph
Me
O
S
NMe
(S)-146
lithiated
(S)-146
OH
Ph
S
NMe
(-)-148a
(+)-148b
toluene,
reflux
(+)-147
(-)-147
OR
149 R = H
150 R = COCH(OMe)Ph
69
112

Syntheses of advanced intermediates in the total synthesis of forskolin

Aside from the three total syntheses of forskolin, a number of reports describing synthetic approaches toward advanced intermediates used in the published schemes have appeared. Among them, the most elegant one was presented by Nicolaou and co-workers (Scheme 2-31).[48] They started from **151**, a product derived from cation-catalyzed cyclization of (*E,E*)-farnesol in 6 steps and about 60% yield, as reported by Corey and McMurry (see Scheme 2-15).[45,46] Oxidative elimination, allylic oxidation and catalytic hydrogenation afforded lactone **152**. Regioselective ketal ring opening with aluminum amide, followed by reclosure with phenylselenenyl chloride, oxidative elimination, reduction of the lactone and removal of the ketal protecting group provided **154**. Protection of the diol as a seven-membered ketal ring, epoxidation of the enone double bond and Wittig reaction to introduce a methylene group yielded **155**, which underwent epoxy-ketone rearrangement, double bond migration and α-epimerization to give **156** Selective reduction of the ketone group, subsequent Sharpless epoxidation, epoxide ring opening and protection of the diol as a ketal furnished **158** (Scheme 2-32). Starting from **158** and following essentially the same sequence as previously described in Ziegler's total synthesis, the Ziegler advanced intermediate **115** was obtained.

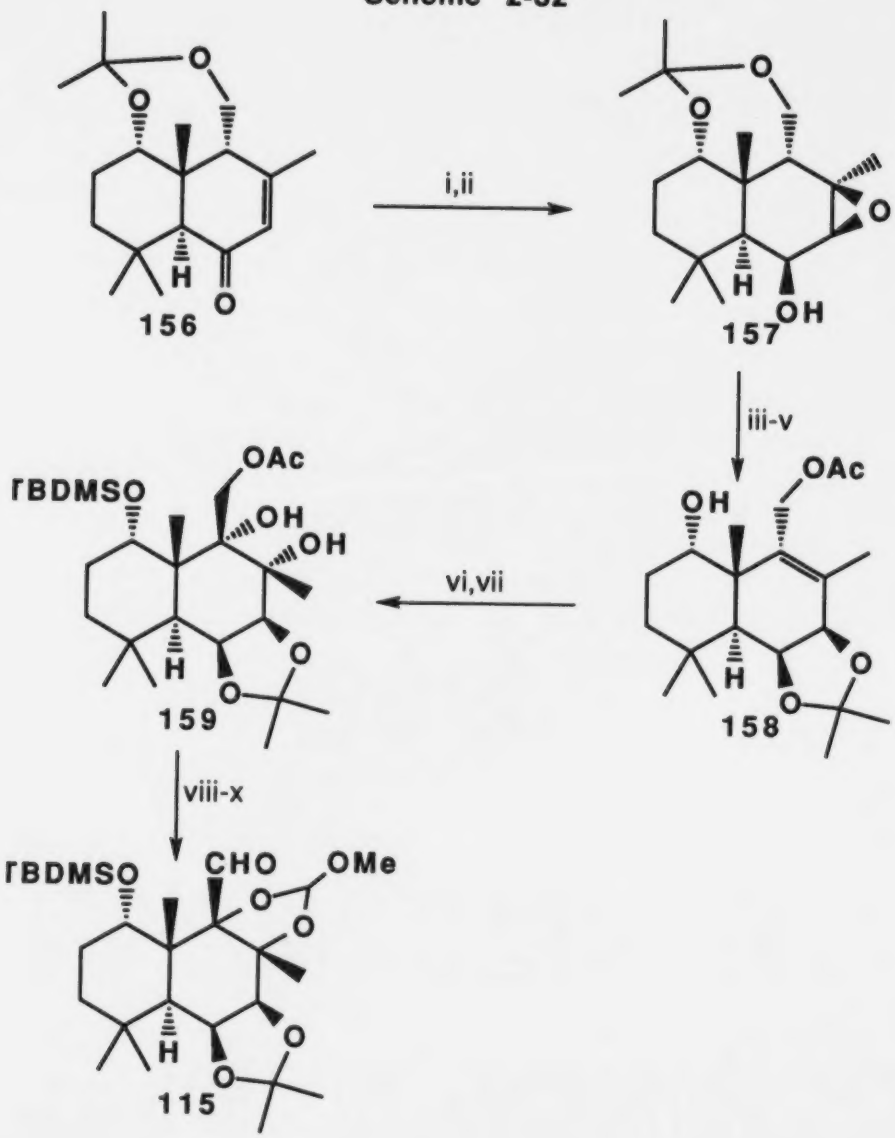
In the last two decades or so, the Lewis acid catalyzed intermolecular Diels-Alder reactions of dienophiles like 164, with or without the second C=C double bond, and their analogs, were extensively studied in our laboratory. These compounds were found to react with a variety of dienes, with a high degree of regio- and stereo-selectivity, to furnish 4,4-dimethyl-1-decalone systems. This type of cycloaddition could also serve as a key step in the

Scheme 2-31



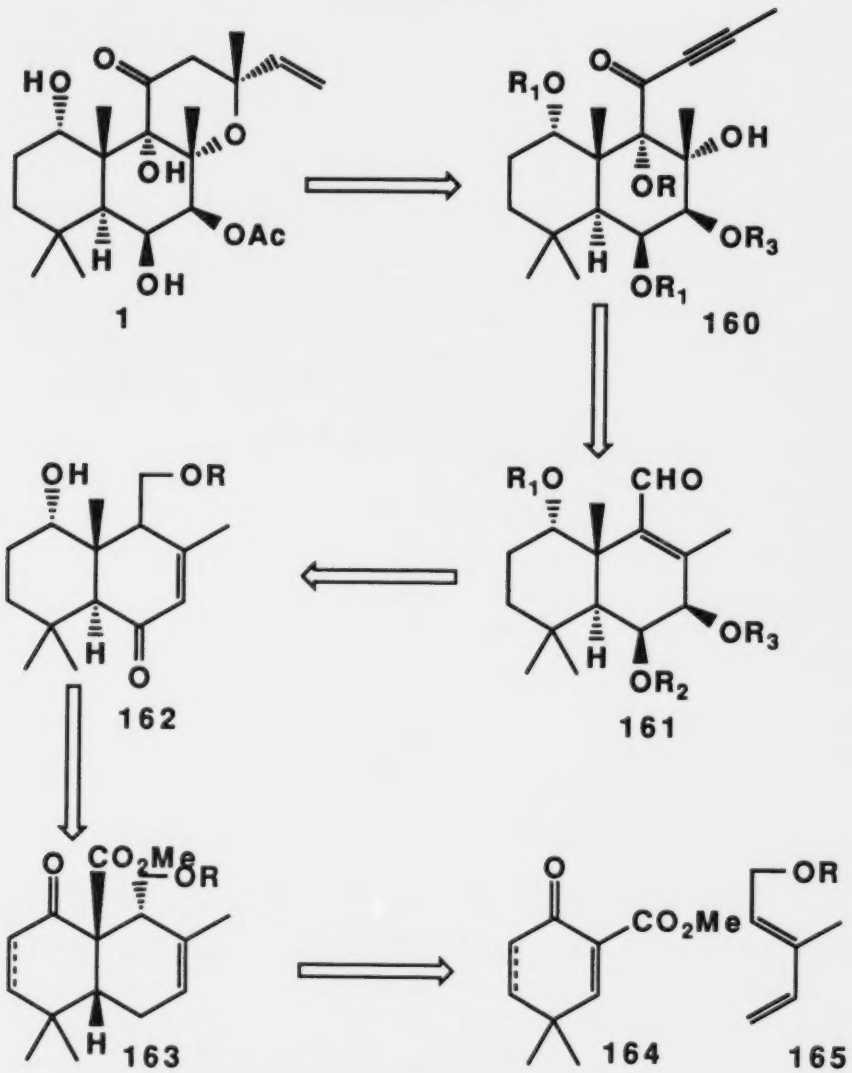
i. O_3, CH_2Cl_2, -78 °C; *i*-Pr_2NH, CCl_4, reflux; ii. SeO_2, dioxane, reflux; iii. H_2, Rh-C, 25 °C; iv. $AlMe_3$, *i*-Pr_2NH, CH_2Cl_2; v. PhSeCl, *i*-$PrNEt_2$, CH_2Cl_2; vi. same as i; vii. $LiAlH_4$, THF; viii. 0.5 M HCl, THF; ix. $Me_2C(OMe)_2$, CSA, CH_2Cl_2; x. 30% H_2O_2, 3 M NaOH, MeOH; xi. $PPh_3P^+MeBr^-$, BuLi, THF, 0 °C; xii. $BF_3 \bullet Et_2o$, CH_2Cl_2, -78 °C; xiii. K_2CO_3, MeOH.

Scheme 2-32



i. DIBAL, THF, -78 °C; ii. $V(acac)_2$, *t*-BuO_2H, PhH, reflux; iii. $Me_2C(OMe)_2$, PPTS, MeOH, 75 °C; iv. MeOH, PPTS, reflux; v. *N*-acetylimidazole, DBU, PhH; vi. OsO_4, Py; vii. *t*-$BuMe_2SiOTf$; viii. $CH(OMe)_3$, *p*-TsOH; ix. $LiAlH_4$, Et_2O, 0 °C; x. CrO_3, Py, CH_2Cl_2.

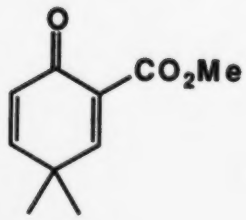
Scheme 2-33



synthesis of forskolin. Cycloaddition of **164** with dienes **165** would give adducts **163**, with all the carbon atoms needed for the A-B rings of forskolin and all the functional groups well positioned for further elaboration. In our approach towards the synthesis of this challenging natural product, intermediate **160**, similar to those in the published total syntheses, was visualized. This

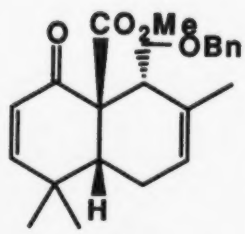
compound could be prepared from **163** by reducing the ketone and the ester to the alcohol and methyl level, respectively, followed by modification of the existing functionalities in ring B.

Dr. N. Al-Said, a former graduate student in our group, did the preliminary studies on the synthesis of forskolin with the dienophile **166** and the diene **167**.[66] He found that, while the $ZnCl_2$-catalyzed Diels-Alder reaction proceeded smoothly to furnish the adduct **168** in excellent yield and the stepwise reduction of the enone **168** ultimately to a diol **169** could be easily carried out, the subsequent deoxygenation of the primary alcohol was problematic. In order to retain the secondary alcohol at C-1, its protection was required. He made use of a "Br^+" induced cyclization and dehydrobromination procedure to obtain an allylic cyclic ether. The 1° alcohol was then reduced *via* Barton's xanthate intermediate to give **170**. Removal of the benzyl group, which was required for the further elaboration of the B-ring, proved, however, to be difficult. In another attempt, he tried to protect the 2° alcohol as a methyl ether and then reduce the 1° one. Selective acetylation of the 1° alcohol to provide **171** was unsuccessful. Mesylation of the 1° alcohol to get **172** was then carried out. But the direct reduction with Zn-NaI or treatment with a base during the protection of the 2° alcohol caused ring fragmentation. Zn-NaI reduction of the keto-mesylate **173** gave decomposed starting material. In light of the difficulties he had encountered, we decided to modify our strategy and to use different protecting groups and approaches. Direct cycloaddition of the free diene alcohol with **166**, followed immediatedly by silylation with TBDPSCl, gave the adduct in good yield. Further elaboration of the existing functionalities gave an endoperoxide lactone **131**, an intermediate appeared in Corey's synthetic scheme (Scheme 2-26). Details are outlined in the second chapter of this thesis.

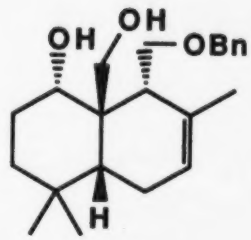


166

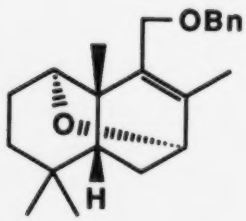
167



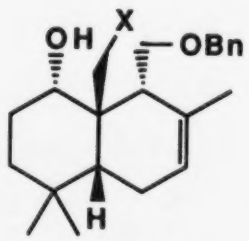
168



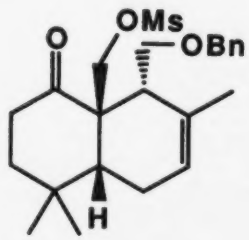
169



170



171 X = OAc
172 X = OMs



173

Results and Discussion

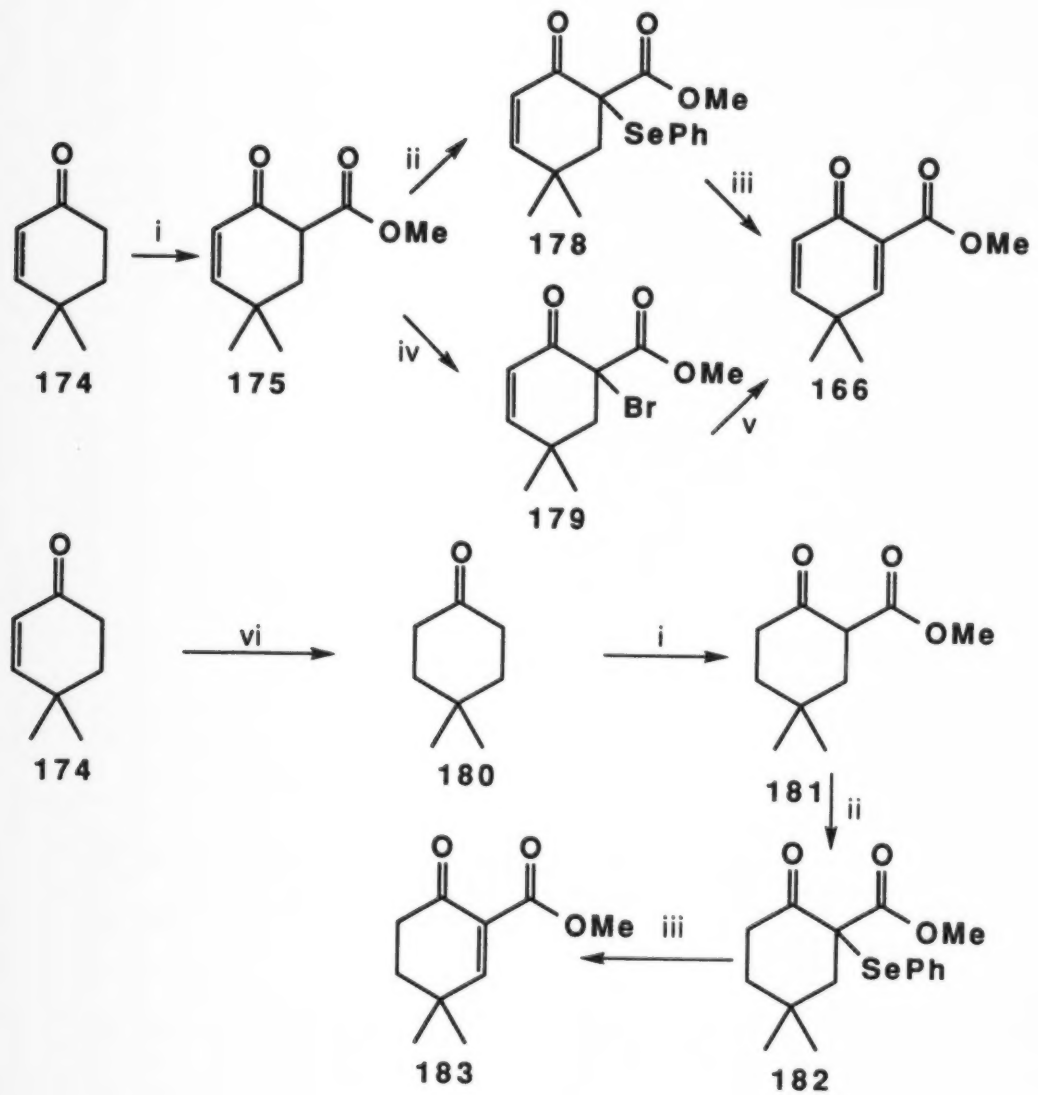
Despite the difficulties Dr. N. Al-Said had encountered in his preliminary work towards the synthesis of forskolin, we remained confident that the intermolecular Diels-Alder approach utilizing dienophiles **164** and dienes **165** was an efficient way to build up the decalin system and set up the stage for later functional group transformations. The major challenge hence became finding the best protecting group for the hydroxy group in the diene. In selecting the protecting group, several criteria had to be met: (1) the protecting group should be easy to put on, (2) stable under the thermal or Lewis-acid-catalyzed Diels-Alder reaction conditions, (3) able to withstand the subsequent functional group transformations before it was removed and (4) should be easily and selectively removed. In Al-Said's work, he used the tris(triphenylphosphine)-rhodium(I) chloride (Wilkinson's catalyst) catalyzed 1,4-addition of triethylsilane and tetrabutylammonium fluoride (TBAF) desilylation sequence to reduce the enone **168** to the corresponding ketone. We also wanted to see if it was possible to use **183**, where the Δ^5 double bond of **166** was absent to begin with, for the Diels-Alder reactions. If successful, the enone reduction step after the cyclization would become unnecessary.

Compound **166** was readily available from 4,4-dimethyl-2-cyclohexen-1-one (**174**) in three steps (Scheme 2-34). Carbomethoxylation with dimethyl carbonate and sodium hydride afforded keto ester **175**. Dienone ester **166** could be prepared from **175** in two ways, either by phenylselenenylation with PhSeCl followed by oxidative elimination without isolating the intermediate **178** or by bromination with *N*-bromosuccinamide (NBS) and subsequent dehydrobromination of the isolated bromide with 1,8-dioazabicyclo[5.4.0]undec-7-ene (DBU).[67] Similarly, the enone ester **183** could be prepared from ketone

180 using the same carbomethoxylation, phenylselenenylation-oxidative elimination sequence.[68] Compound **180**, in turn, was readily prepared from enone **174** by catalytic hydrogenation. For the conversion of keto ester **181** to enone ester **183**, the bromination-dehydrobromination method was not effective. A messy reaction mixture resulted during the dehydrobromination step, probably due to side reactions like Favorskii rearrangement involving the α-bromoketone.

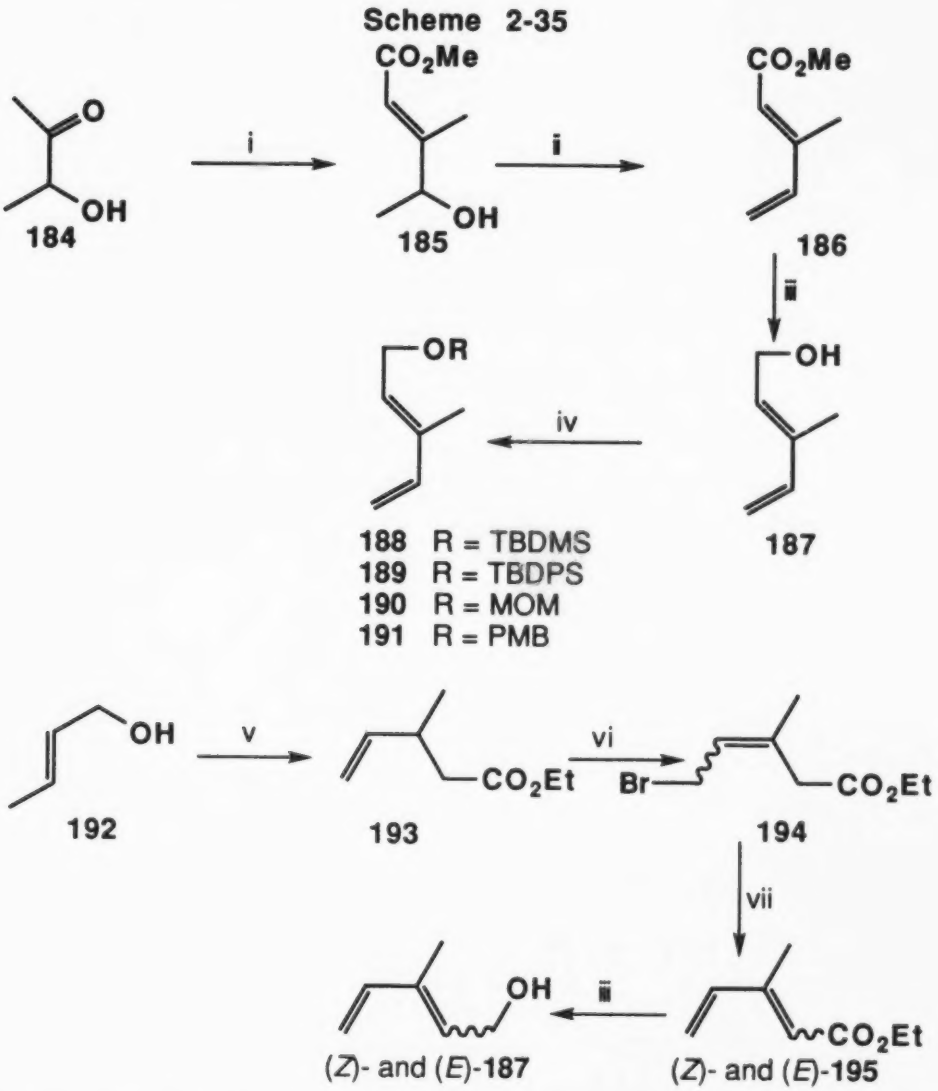
The dienes (**187** - **191**) with a free or protected hydroxy group could be prepared mainly in the *E*-forms (*E* : *Z* ≥ 17 : 1) by applying a Wittig reaction to 3-hydroxy-2-butanone (**184**) with methyl (triphenyl-phosphoranylidene)acetate (Scheme 2-35). Subsequent dehydration and $LiAlH_4$ reduction furnished the free alcohol **187**.[66] The protection of the free hydroxy group could be achieved in various forms with a suitable halide in the presence of an adequate base. It was found in our previous experiments that when both of the *E*- and *Z*-isomers of the ester **186** or the benzyl ether **167** were used directly for the [4 + 2] cyclization reactions, the *Z*-isomer in each case was much less reactive than the corresponding *E*-isomer. This is primarily due to their reluctance to adapt the *s*-cisoid conformation which is a prerequisite for the occurrence of this type of cycloaddition. A mixture of the *Z*- and *E*-**187** was also prepared using the orthoester Claisen rearrangement protocol developed in our group. Crotyl alcohol **192** and a catalytic amount of propionic acid in neat triethyl orthoester at 128 °C provided ethyl 3-methyl-4-pentenoate **193**. Free radical bromination with NBS gave the allylic bromide **194**, which, upon dehydrobromination, furnished a mixture of *E*- and *Z*-diene ester **195** in a ratio of around 3 : 1. Compounds **195** were in turn reduced with $LiAlH_4$ to give the corresponding alcohols **187**.[69]

Scheme 2-34



i. $(MeO)_2CO$, NaH, DME; ii. PhSeCl, Py, CH_2Cl_2; iii. H_2O_2; iv. NBS, CCl_4; v. DBU, PhH; vi. Pd / C, H_2.

Scheme 2-35



i. $Ph_3P{=}CHCO_2Me$, PhH; ii. anhydrous $CuSO_4$; iii. $LiAlH_4$, Et_2O; iv. base, RX; v. $CH_3C(OEt)_3$, propionic acid, 128 °C; vi. NBS, AIBN, CCl_4; vii. $NaOCMe_3$, $HOCMe_3$.

To compare the reactivities of the two dienophiles, **166** and **183**, the same diene **167** was subjected to anhydrous $ZnCl_2$ catalyzed Diels-Alder reactions. The reaction with the dienone ester **166** proceeded smoothly as previously observed by Al-Said,[66] giving 74% of *endo*-to-ketone adduct after

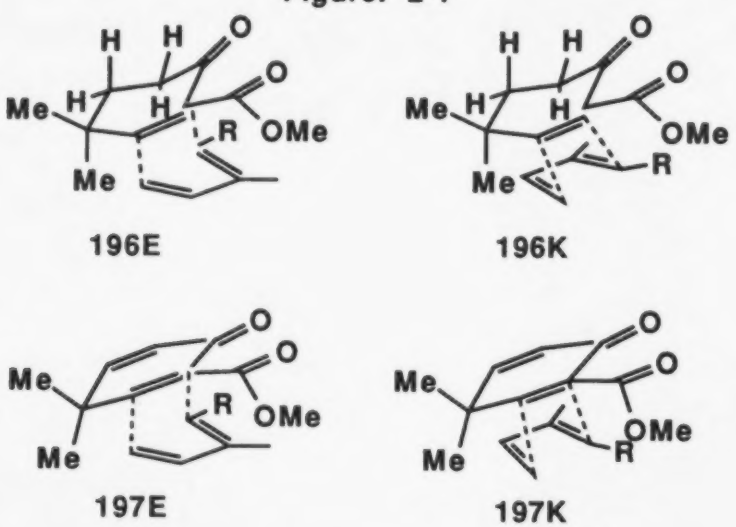
stirring for 3 days in dichloromethane at room temperature. The reaction with **183** was much slower, giving the desired adduct in 57% yield along with a recovery of 43% of the dienophile. In ether, there was no reaction at all between **183** and **166**.

Despite the slower rates of reaction associated with **183**, we decided to investigate the reactions of this dienophile with assorted dienes under thermal conditions or catalysis with different Lewis acids. The first protecting group that was tested on the diene part was the*t*-butyldimethylsilyl (TBDMS) group, since it was relatively less bulky and yet reasonably stable. Under the catalysis of 2.5 equivalents of anhydrous $ZnCl_2$ in CH_2Cl_2 at room temperature or in refluxing xylene, no adduct was observed in the ^1H NMR spectrum of the crude reaction mixtures. No starting diene was recovered due to decomposition. This was a clear indication that the protecting group was not suitable under these reaction conditions and it was also indicative of the slower reaction rate between this pair of dienophile and diene.

To increase the stability of the diene, the *t*-butyldiphenylsilyl (TBDPS) group was used in place of the TBDMS. After 40 hr in refluxing toluene, 5% of *endo*-to-ketone adduct was isolated, together with 87% of the recovered dienophile. However, partial decomposition of the diene was observed. In an attempt to increase the yield and rate of the reaction, toluene was replaced by xylene. After refluxing for 3 days, no product was observed and the diene was completely destroyed. Under the catalysis of $ZnCl_2$ at room temperature, or $FeCl_3$ at between -30 °C and 10 °C, no adduct was observed and the diene was totally decomposed. These results suggested to us that replacing the TBDMS group with the TBDPS group did help to increase the stability of the diene slightly. The slow reaction rate and poor stability of the diene, however, suggested its limited applicability in any synthetic scheme.

The unprotected alcohol **187** was sterically least hindered. As such, it could also form a tighter complex with a Lewis acid. Both of these factors would contribute to an increase in the reaction rate. Hence we decided to use the unprotected alcohol as the diene. With $ZnCl_2$ as the catalyst, only a very messy reaction mixture was obtained. It was obvious that either the diene, the product or both of them were unstable under this condition. The same phenomenon was observed with dienophile **166**. A rationale will be offered later.

Figure. 2-1



The results with dienophile **183** were disappointing but nevertheless interesting in terms of the stereochemistry of the products. According to my results, no major switch-over from *endo*-to-ketone to *endo*-to-ester in the transition states was observed when **183** was used in place of **166** (Figure 2-1). The favorable transition state was **196K**, as was **197K** for the dienone-ester **166**. The ester group at C-10 was always *trans* to the alkyl group at C-9. It would be reasonable to predict that with **166**, the reaction rates would be faster. The introduction of the secondary orbital interaction with the second C=C double bond and the disappearance of the unfavorable steric interaction

between the quasi-axial hydrogen atoms at C-5 and C-6 and the dienes would help to lower the energy of the transition states. Based on this consideration, we decided to go back to dienone-ester **166**.

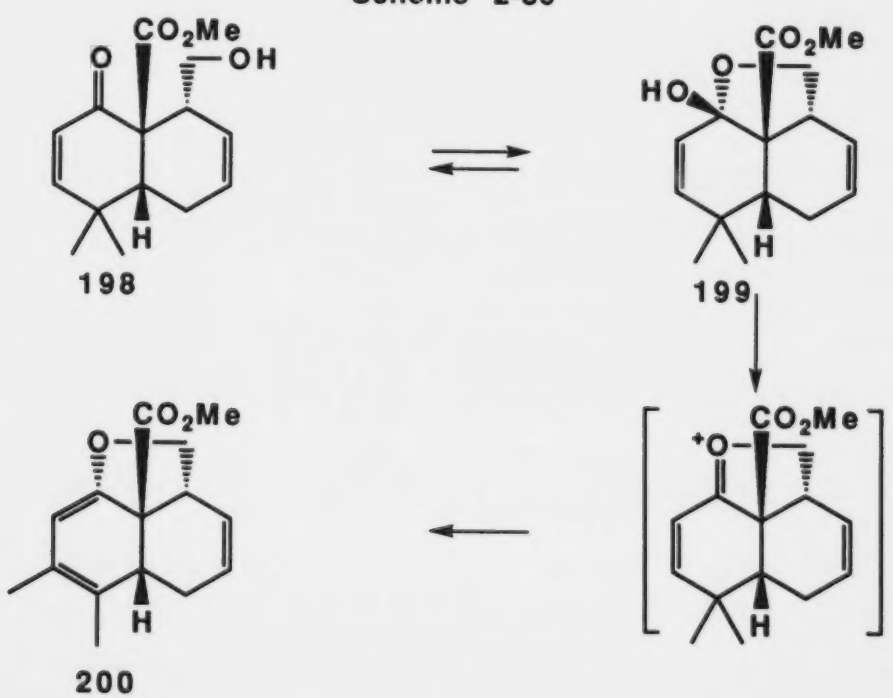
At that moment, we were still faced with the dilemma of finding a suitable protecting group for the diene. *t*-Butyldiphenylsilyl ether seemed to be the best choice, since it was more stable under the Diels-Alder reaction conditions than *t*-butyldimethylsilyl ether and it would be easily and selectively removed with fluoride ion. Thermal cycloaddition between enone-ester **166** and diene **189** in refluxing toluene did not show any promising sign, as no product was observed and the diene was partially decomposed. Zinc chloride catalyzed cycloaddition in CH_2Cl_2 at room temperature gave only 27% of the adduct with complete disappearance of the diene. Changing the solvent to ether slowed down the Diels-Alder reaction as well as the diene decomposition. Increasing the temperature was not helpful. When anhydrous $FeCl_3$ was used as the catalyst, the diene decomposed instantly at 10 °C. When the reactions were run with stannous(IV) chloride in ether at temperatures ranging from -15 °C to room temperature, the highest yield obtained was 27% and the remaining diene decomposed.

Dienes with other protecting groups, like methoxymethyl (MOM) ether and *p*-methoxybenzyl (PMB) ether were also tested. Those dienes were very unstable under $ZnCl_2$ catalysis and decomposed very rapidly. No desired products were ever isolated.

This was the dilemma which we often encountered with unstable dienes. The decomposition of the diene was competing with the cyclization process. We could succeed only if the latter process was far more rapid than the former one.

Reaction with unprotected diene-alcohol **187** under the catalysis of $ZnCl_2$ was attempted. Since this diene was sterically less demanding and could form a tighter complex with the Lewis acid, we expected that the Diels-Alder reaction would be fast enough to outpace the decomposition process. Under the catalysis of $ZnCl_2$ at room temperature in CH_2Cl_2, this was actually true. A major spot was found on the t.l.c. plate along with some minor ones. Column separation gave a major fraction **201**, which turned into a mixture of several compounds upon standing at room temperature. This resembled exactly what Al-Said had observed with a similar compound **198** (Scheme 2-36). He realized that the semiacetal formation, catalyzed by trace amount of acid or base, would give **199**. Compound **199** could either go back to the starting ketone or be transformed further into **200** under acid catalysis. Compound **200** was actually isolated and characterized.[66]

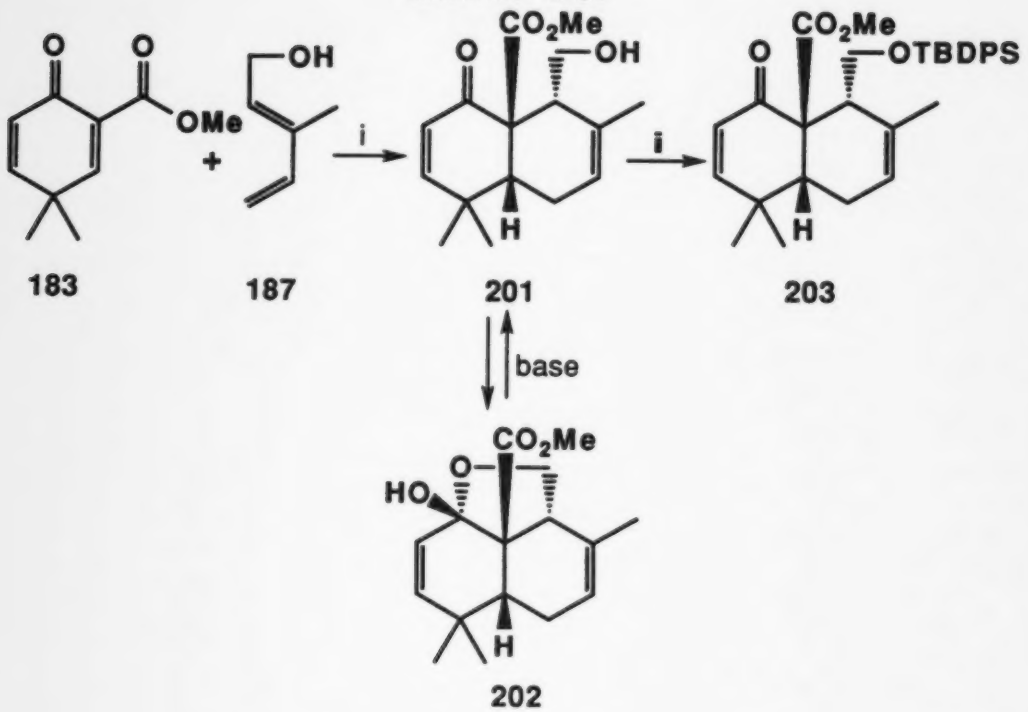
Scheme 2-36



Similarly, our adduct **201** would also cyclize reversibly to give the semiacetal **202** (Scheme 2-37). Under neutral or slightly basic conditions, the formation of the dehydration-rearrangement product should have been suppressed or avoided. The crude Diels-Alder reaction mixture was treated directly with *t*-butyldiphenylsilyl chloride with excess imidazole in DMF at room temperature. The primary alcohol in **201** would react at a much faster rate than the congested tertiary alcohol of the semiacetal in **202**. By shifting the equilibrium between **201** and **202** towards **201**, most of **201** and **202** would eventually be silylated. During the work-up, methanol was added to the reaction mixture to destroy excess *t*-butyldiphenylsilyl chloride resulting in the formation of a methyl silyl ether, as the silanol derived from the reaction with water hindered the separation of the desired product, due to their close R_f values. Compound **203** was isolated in 64% overall yield for the cycloaddition and silylation steps.

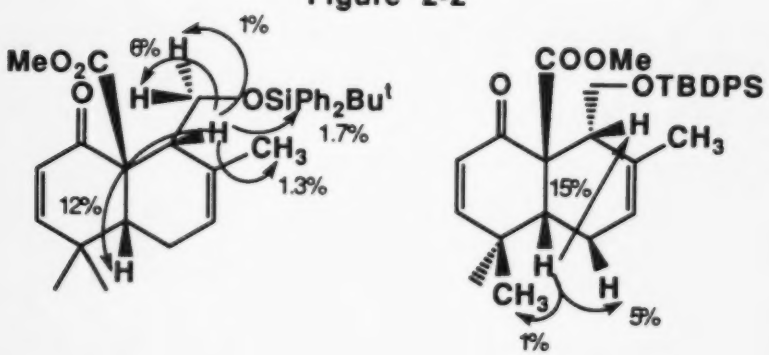
The IR spectrum of **203** showed two strong carbonyl bands at 1732 and 1691 cm^{-1}, indicative of the ester and the enone, respectively. In the ^1H NMR spectrum, the α- and β-protons of the enone and the olefinic proton on ring B resonated at 5.82 (doublets), 6.22 (doublet of doublets) and 5.23 ppm (a broad singlet), respectively. The *t*-butyldiphenylsilyl group was represented by the aromatic protons at around 7.62 and 7.35 ppm and the singlet at 1.04 ppm for the *t*-butyl group. The methyl ester appeared at 3.33 ppm as a sharp singlet. The resonance signals were assigned based on decoupling experiments and coupling constant correlations. The *trans*-relationship of the siloxymethyl group at C-9 to the ester group at C-10 and the angular proton at C-5 was determined by NOE experiments, as shown in Figure 2-2.

Scheme 2-37



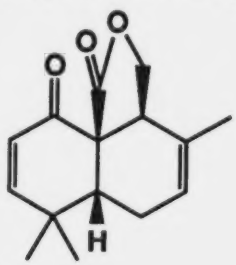
i. $ZnCl_2$, CH_2Cl_2, r.t.; ii. TBDPSCl, imidazole, DMF, r.t.

Figure 2-2



It is noteworthy that, when a mixture of (*E*)- and (*Z*)-**187** (2.2 : 1) was used in place of pure (*E*)-**187** for the same cycloaddition-silylation sequence, **203** and enone-lactone **204** were obtained in a ratio of 4 : 1. This result

suggested that while the (*E*)-isomer was still more reactive than the (*Z*)-isomer, the gap in reactivity was narrowed to 1.8 : 1. Compound **204** differed from **203** in the disappearance of the methyl group of the ester and the *t*-butyldiphenylsilyl group and the formation of the lactone ring. Two characteristic carbonyl bands for the lactone and enone appeared at 1770 and 1673 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum, the α– and β-protons of the enone and the olefinic proton of the double bond on the B-ring appeared as a doublet, a doublet of doublets and a broad multiplet at 5.80, 6.52 and 5.19 ppm, respectively. The two methylene protons of the lactone ring resonated at 4.84 and 4.29 ppm. High resolution mass spectrometry gave the molecular ion at m/z 246.1259 (calcd. for $C_{15}H_{18}O_3$: 246.1256).

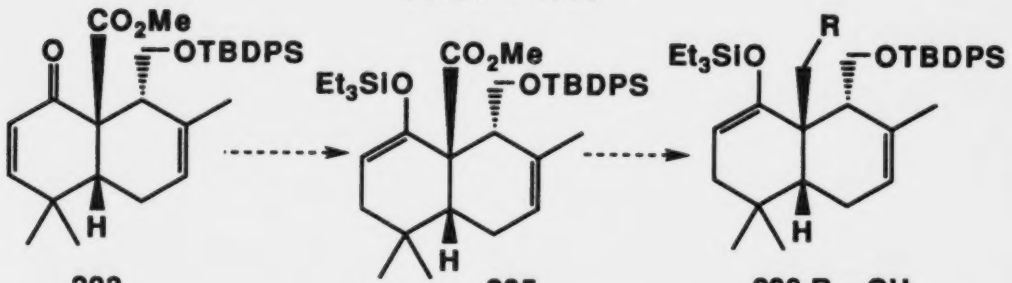


204

Our retro-synthetic scheme called for the reduction of the enone to a ketone and the angular ester group to a methyl group. Al-Said reduced the enone with the hydrosilylation-desilylation sequence. It would be advantageous to use the hydrosilylation product **205** directly without desilylation for the subsequent reduction of the ester to obtain **206** (Scheme 2-38). The hydroxyl group could then be reduced by first converting it into **207** (where R = OMs, OC(S)SMe, OC(S)OPh, $OP(O)(NMe_2)_2$, *etc.*) and then replaced with a hydrogen atom to afford the angular methyl group. This was attempted with the crude hydrosilylation product for $LiAlH_4$ reduction. A very

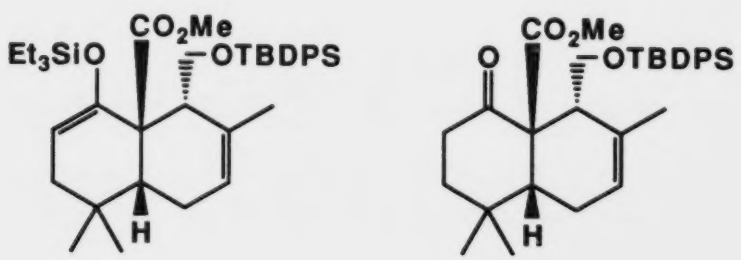
messy product mixture was obtained, due to the instability of the silyl groups to the hydroxide or alkoxide introduced or produced during the hydride reduction step. This route was abandoned.

Scheme 2-38



203 **205** **206 R = OH**
207 R = OX
208 R = H

Reduction of the enone **203** to the ketone **209** was then pursued. Hydrosilylation with Et_3SiH under the catalysis of Wilkinson's catalyst in benzene at 50 °C gave a mixture of silyl enol ether **205** (48%) and the ketone **209** (35%). General desilylation with fluoride could not be applied to **205** because of the presence of the TBDPS group. Selective removal of the triethylsilyl group with K_2CO_3 in methanol at room temperature resulted in a complex mixture again.



205 **209**

Djerassi and Gutzwiller reported that, with Wilkinson's catalyst, enones like Δ^1-3-keto-steroids were readily hydrogenated, while Δ^4-3-keto-steroids

were recovered unchanged.[70] Compound **203** resembled those Δ^1-3-keto-steroids, therefore, its homogeneous hydrogenation was expected to provide **209**. Hydrogenation with Wilkinson's catalyst (0.1 eq) in benzene or methanol at 2 atm for 5 days failed to deliver any hydrogenated product **209**. This implied that our enone system was extremely hindered.

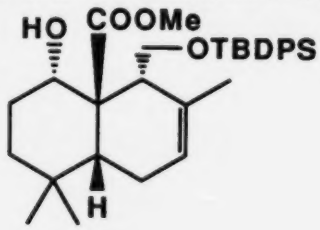
Keinan's three-component system, which comprised tetrakis-(triphenylphosphine)palladium(0), zinc chloride and a hydrosilane like diphenylsilane, was found to be less sensitive to steric effects.[71] Even those trisubstituted C=C double bonds in Δ^4-3-keto-steroids were reduced to produce mixtures of 5α- and 5β-*H*-3-keto-steroids. When the reaction with **203** was run with 0.01-0.02 equivalent of $(Ph_3P)_4Pd(0)$, it was extremely slow. When the amount of the palladium catalyst was raised to 0.1 equivalent, 60% of the desired product was isolated, together with 25% of recovered starting material **203**. Prolonged stirring under Ar also produced other side products.

As a useful reducing agent, the hexamer of (triphenylphosphine)copper-hydride, $(Ph_3PCuH)_6$, was developed by Stryker and co-workers.[72] It was very effective and yet selective in reducing the C=C double bonds of conjugated ketones, aldehydes, esters, nitriles, sulfones and sulfonates. Isolated olefins, carbonyls, halogens and typical oxygenated functionalities were not reduced. With our sterically hindered enone **203**, an excess amount, usually of around 0.8 mole (4-5 equivalents of hydride), of the reagent was needed to drive the reaction to completion in 4 days. The isolated yield of **209** was 99%. In the IR spectrum, the bands for the carbonyls of the ester and the ketone merged together as a strong and broad band at 1721 cm^{-1}. In the ^{13}C NMR spectrum, the ketone and ester carbonyl carbons appeared at 208.23 and 174.69 ppm, respectively.

Reduction of the keto group of **209** was first attempted with $NaBH_4$. The substrate **209** was relatively non-polar and its solubility in alcoholic solvents like isopropanol or methanol was rather low. It was hard to find a common solvent that would dissolve well both of enone **209** and $NaBH_4$. .

Heating **209** with L-selectride in THF at 40 °C did not produce any product and the starting material was recovered unchanged.

Lithium tri-*tert*-butoxyaluminohydride, $LiAl(OBu^t)_3H$, turned out to be a perfect reagent for reducing the ketone into the α-alcohol. Due to its sheer size and ability to coordinate with the carbonyl oxygen of the ester group, the hydride reduction went exclusively from the β-face to provide the α-alcohol **210** in 98% yield with virtually no detectable amount of the β-isomer.



210

For **210**, a broad IR absorption band at 3510 cm^{-1} indicated the presence of a H-bonded hydroxy group, and the strong absorption at 1720 cm^{-1} suggested that the ester remained intact. In the ^1H NMR spectrum, the α-proton of the alcohol appeared at 4.60 ppm as a broad singlet. The presence of the ester group was evidenced by the methyl singlet at 3.54 ppm.

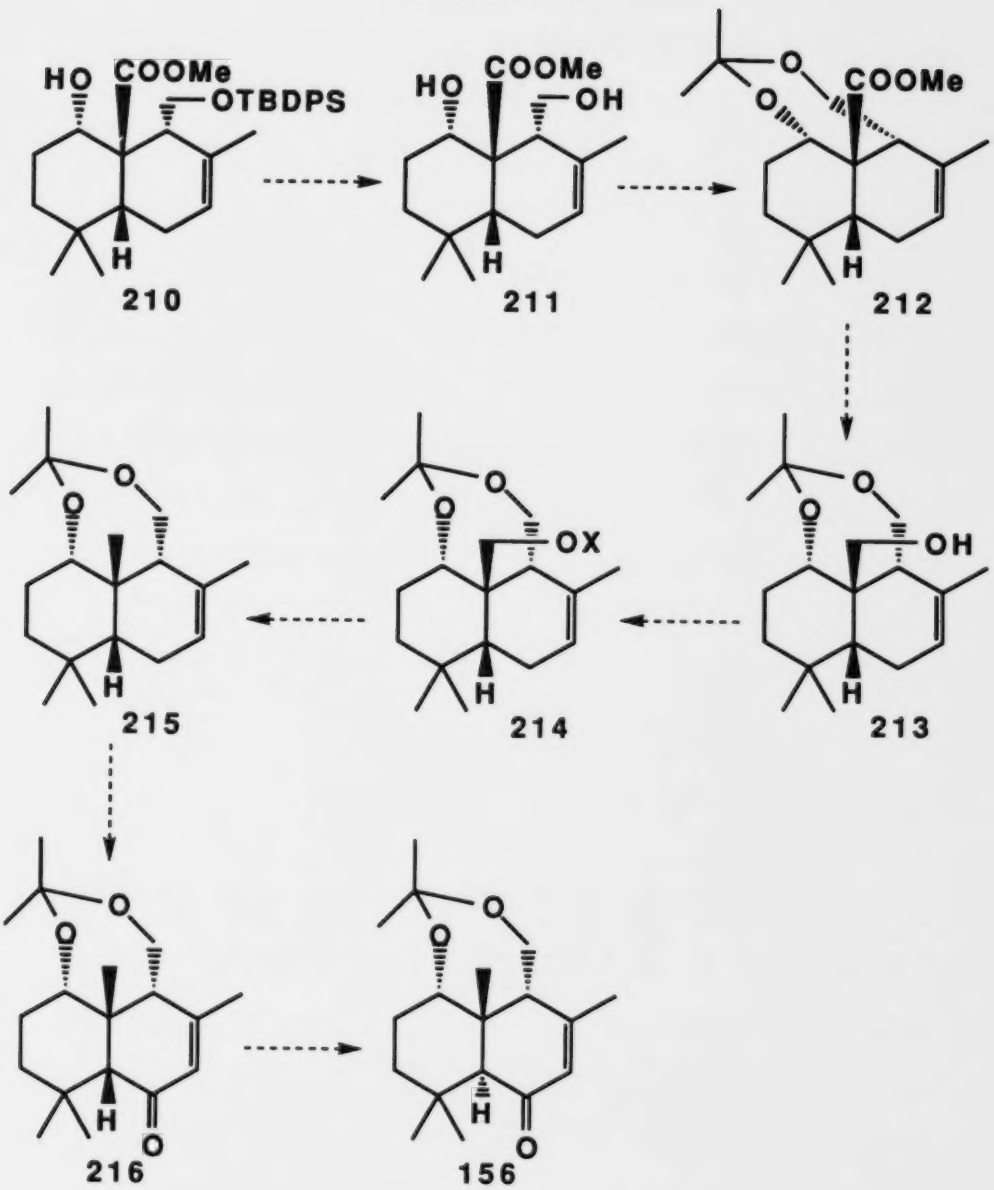
At this point, a suitable protecting group for the C-1 hydroxy group needed to be found that would survive all of the ester group reduction and subsequent deoxygenation reaction conditions. An ether group or acetal group would be adequate. At the same time, we were planning to pursue the synthesis of forskolin *via* some advanced intermediates found in the published

total syntheses, instead of the final target, forskolin. Nicolaou's intermediate **156** was a good candidate. It took them 19 steps to prepare **156** in an overall yield of 18%, starting from a natural product, (*E,E*)-farnesol. A shorter route was envisioned to convert **210** to **156** (Scheme 2-39). Removal of the silyl ether protecting group followed by acetal formation would protect the diol from any reductive, basic or neutral conditions required for the conversion of the ester group to a methyl group. Introduction of oxygen at C-6, followed by epimerization at C-5, if necessary, would provide **156**.

Removal of the silyl group was straightforward. Treatment of **210** with tetrabutylammonium fluoride (TBAF) in THF at room temperature furnished **211** in 96% yield. Its IR spectrum had a broad and strong absorption band at 3257 cm^{-1}, due to the two hydroxy groups. In the ^1H NMR spectrum, the two hydrogens on the hydroxy groups appeared at 2.90 ppm as a broad singlet, which disappeared upon addition of D_2O.

The preparation of the acetonide **212** was troublesome at first. A chemical Abstracts on-line search revealed that, if prepared, **212** would be the first 7-membered cyclic acetal ring fused with a *cis*-decalin system at the C-1 and C-9 positions, let alone with all the substituents present. The acetonide ring was bent into the concave side of the cup-like *cis*-decalin skeleton, making this structure extremely crowded. This compound would be difficult to make. Once made, it would be very unstable when a trace amount of acid was present. The first few attempts to prepare **212** with acetone under *p*-TsOH catalysis or with 2,2-dimethoxypropane and a catalytic amount of *d*-10-camphorsulfonic acid (CSA) all led to failure. Finally, treating **211** in neat 2,2-diethoxypropane in the presence of CSA at room temperature under reduced pressure (50 torr) furnished **212** in 96% yield. At this temperature and vacuum, the side-product ethanol was pumped away while the reagents stayed.

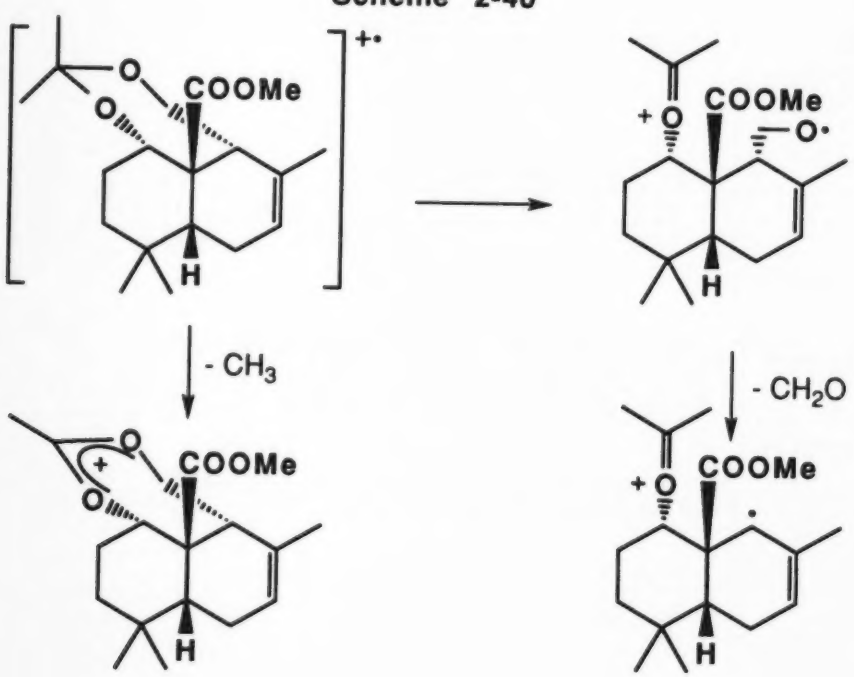
Scheme 2-39



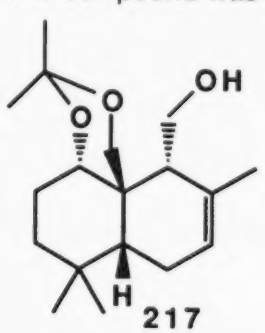
The ^{1}H NMR spectrum of **212** displayed five singlets for methyl groups attached to carbon atoms at 1.72, 1.42, 1.26, 0.92 and 0.90 ppm and one singlet at 3.63 ppm for the ester methyl group. The ^{13}C NMR spectrum gave four resonance signals at 178.79, 131.37, 124.45 and 100.19 ppm, for the carbonyl

of the ester, the two carbons of the C=C double bond and the quaternary carbon of the acetonide, respectively. In the IR spectrum, the ester carbonyl manifested itself at 1718 cm^{-1} as a strong and sharp band. The molecular ion appeared in high resolution mass spectrometry at 322.2115 (calcd. for $C_{19}H_{30}O_4$: 322.2144). Ions at m/z 307.1905 ($M^+ - CH_3$, calcd. for $C_{18}H_{27}O_4$: 307.1910) and 292.2014 ($M^+ - CH_2O$, calcd. for $C_{18}H_{28}O_3$: 292.2039) were also present and were persistent features of all those seven-membered ring acetonides, as would be observed later. The $M^+ - 15$ ion was due to the loss of one of the two methyl groups on the α-carbon of the acetal group (Scheme 2-40). The $M^+ - 30$ ion was caused by the opening of the highly strained acetonide ring, followed by the loss of formaldehyde to end up with an allylic radical and oxonium ion. Sometimes there fragmentation were so favorable that the molecular ions could not be observed.

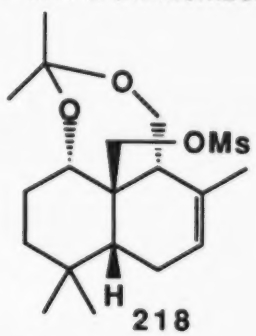
Scheme 2-40



Reduction of **212** with lithium aluminum hydride in ether at room temperature was very straightforward and afforded alcohol **213** in 100% yield. The α–methylene group of the alcohol appeared in the ^1H NMR spectrum at 3.33 and 3.31 ppm as a pair of doublet of doublets, due to couplings between themselves and with the proton on the hydroxy group. The D_2O exchangeable pseudo triplet at 3.96 ppm indicated the presence of the hydroxy group. The acetal group remained intact, as evidenced by the five singlets for the methyl groups between 1.7 and 0.7 ppm. The IR spectrum gave a broad, medium absorption at 3428 cm^{-1} due to the hydroxy group. High resolution mass spectrometry failed to deliver the molecular ion for $C_{18}H_{30}O_3$, but gave the $M^+ - CH_2O$ peak at 264.2086 (calcd. for $C_{17}H_{28}O_2$: 264.2089). Chemical ionization mass spectrometry gave the $M^+ + 1$ ion at 295.1. Compound **213** was found to be relatively stable in its solid state or in solvents like acetone. In $CDCl_3$ and with the presence of a trace amount of acid, it slowly rearranged to give another acetonide, as was observed in the ^1H and ^{13}C NMR spectra. The rearrangement product resembled **213** in its ^1H and ^{13}C NMR spectra. Considering the highly unstable nature of the seven-numbered ring in **213**, it was assumed that this compound was **217** with a six-membered acetal ring.



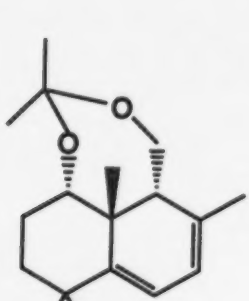
217



218

To deoxygenate **213**, the corresponding mesylate **218** was first prepared in 90% yield with mesyl chloride and triethylamine. Its ^1H NMR

spectrum gave the methyl group of the mesylate at 3.13 ppm as a singlet and the two methylene protons adjacent to the mesylate as two doublets at 3.96 and 3.71 ppm. The acetal group was intact, as evidenced by the five methyl groups at 1.73, 1.28, 1.24, 1.16 and 0.98 ppm. The IR spectrum displayed the typical absorptions for the mesylate at 1355, 1220 and 1177 cm^{-1}. High resolution mass spectrometry failed to register the molecular ion peak, but chemical ionization mass spectrometry did give the $M^+ + 1$ peak at 373.4. The $M^+ - CH_2O$ fragment appeared at 342.1865 (calcd. for $C_{18}H_{30}O_4S$: 342.1865).



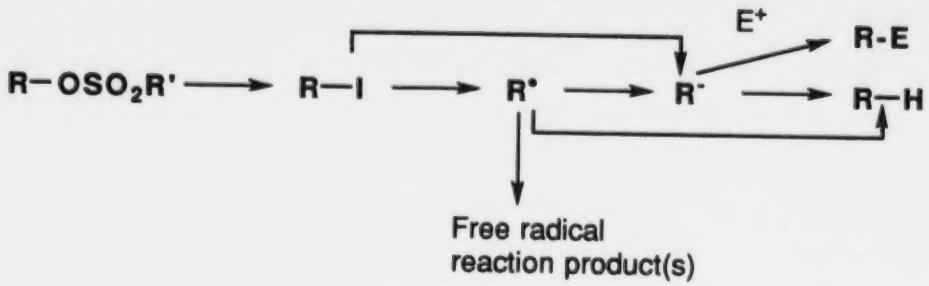
219

It was well established that a combination of zinc dust and sodium iodide was able to reduce mesylate to the corresponding alkanes.[73] This method was applied here. Heating **218** with zinc dust and NaI in DMF at 110 °C afforded quite unexpectedly diene **219** in 86% yield. This compound was visible on the t.l.c. plate under a UV-254 lamp. In the ^1H NMR spectrum, the olefinic protons appeared at 5.76 and 5.58 ppm. The mesylate C-OMs was successfully reduced to C-H, as there were in total six methyl groups, as proved by the six singlets at 1.74, 1.32, 1.25, 1.16, 1.15 and 1.02 ppm. In the ^{13}C NMR spectrum, there were four peaks at 152.57, 135.40, 124.85 and 123.16 ppm, corresponding to the four sp^2 carbons of the diene. High resolution mass

spectrometry displayed the M^+ ion and $M^+ - CH_2O$ ion peaks at 276.2083 (calcd. for $C_{18}H_{28}O_2$: 276.2089) and 246.1978 (calcd. for $C_{17}H_{26}O$: 246.1978).

This unexpected result prompted us to look further into the mechanism of this type of reactions. Reduction of mesylates or tosylates with zinc powder and sodium iodide in DME was first discovered by Fujimoto and Tatsuno in 1976.[73] It was suggested and generally accepted that the mesylates R-OMs or tosylates R-OTs first underwent substitution reactions to produce the iodides, which accepted an electron from zinc to give a radical (Scheme 2-41). Transfer of another electron to the radical would result in a carbanion, as in organozinc compounds. Quenching the reaction with a proton source would provide the reduced product, R-H.[74] Modified sequences, wherein the radical R· was bypassed by a rapid two-electron reduction of R-I by zinc or the formation of anion R^- was excluded by hydrogen atom abstraction by the radical R·, were also considered possible, although no investigation to this end was ever attempted or any evidence obtained. The intermediacies of the radical and the organozinc carbanion were observed. Pradhan and co-workers found that besides the normal reduction products, products derived from typical intramolecular radical addition to unactivated double or triple bonds were isolated.[75] Knochel *et al.* developed a general methodology based on this reaction. They treated organic chlorides, bromides, sulfonates and phosphates with excess zinc powder and a catalytic amount of alkali metal iodide (M = Li, Na, Cs) in a polar solvent like *N,N*-dimethylpropyleneurea (DMPU) or *N,N*-dimethylacetamide (DMA). The resulting organozinc compounds were reacted with electrophiles such as Michael acceptors to produce the expected products.[76]

Scheme 2-41

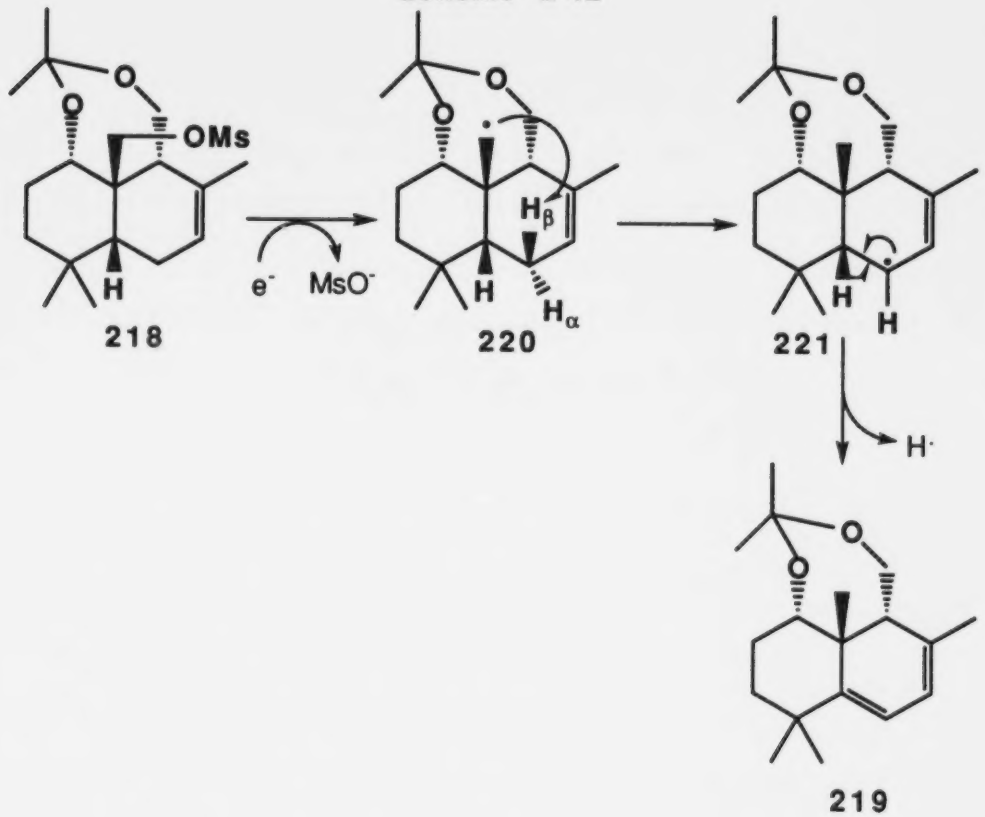


The above proposed mechanism is not free of controversy. With sterically hindered mesylates and under similar conditions with excess sodium iodide and without zinc powder, no substantial amount of iodide was isolated. It still remains unclear as to the nature of the real electron transferring agent. Is it just zinc metal or some kind of active zinc or activated form of zinc? Is it possible that sodium iodide is involved in the activation or production of the active form of zinc, which would be able to insert into the R-OMs bond?

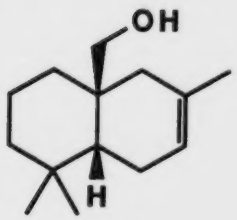
As to the formation of **219**, it seemed likely that the radical species **220** was playing a central role (Scheme 2-42). One electron transfer to the mesylate group or the corresponding iodide, followed by the loss of the mesylate ion or iodide, would give **220** with a radical on the methylene group. This radical could receive another electron to become an anion, or abstract a hydrogen atom from the other part of the molecule. The β-hydrogen at C-6 is in the vicinity and within its reach. The intramolecular hydrogen abstraction process was much faster than the second intermolecular electron transfer, especially with a moderately reactive, slow reacting metal like zinc. It would be possible to avoid the formation of the diene if a much higher concentration of "electron" or a much more reactive metal was present. Intermediate **221**, after giving away the hydrogen atom at C-5 to the media, would produce **219**. This is only an

explanation rather than an proved, detailed mechanism. Other postulation may also be offered.

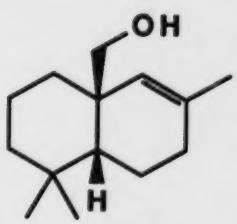
Scheme 2-42



As far as we know, this was the first known case of what appeared to be an oxidative double bond formation under the Zn-NaI reductive conditions. We decided to investigate the case using compounds with similar structural features, namely, the *cis*-decalin system possessing the angular mesyloxylmethyl group and a double bond on the B-ring.

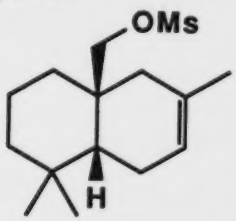


222

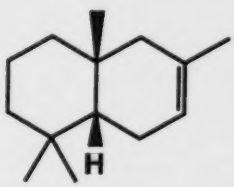


223

Compounds **222** and **223** were prepared as a mixture by Gerardo Ulibarri, a former Ph.D. student in our group, during his total synthesis of (±)-isoacanthodoral.[67] These two compounds were isolated in pure forms from the mixture and were subjected to mesylation reactions to prepare the corresponding mesylates.



224



225

Mesylation of **222** proceeded smoothly to provide **224** in 90% yield. In the ^{1}H NMR, the formation of the mesylate was evidenced by the presence of a singlet at 2.98 ppm for the mesylate and two doublets at 3.96 and 3.88 ppm for the two methylene protons adjacent to the mesyl group. The IR bands of the mesylate group appeared at 1355 and 1176 cm^{-1}. High resolution mass spectrometry gave the molecular ion at 286.1599 (calcd. for $C_{15}H_{26}O_3S$: 286.1603). Reduction of **224** with zinc and sodium iodide gave the expected "normal" product **225** as the only product in 41% yield. No product was found that showed a UV absorption under a UV-254 lamp. The low yield of **225** was probably due to its high volatility. Compound **225** has four methyl groups, as

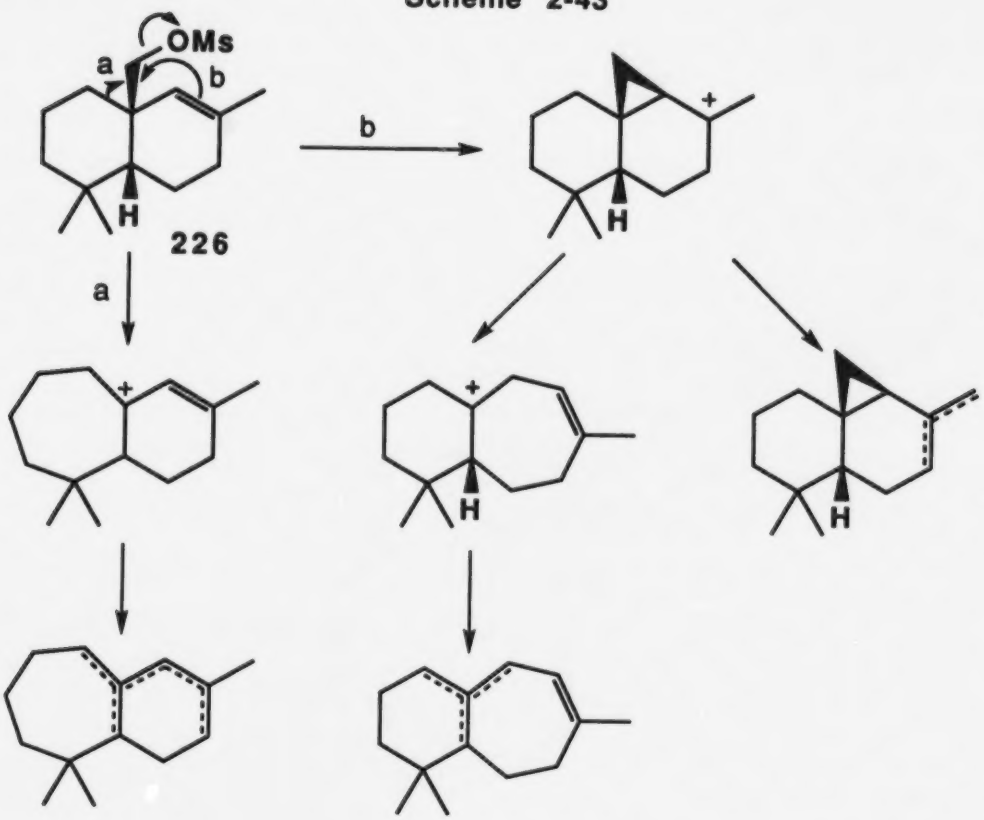
demonstrated by the four singlets at 1.61, 0.90, 0.86 and 0.76 ppm in the ^1H NMR spectrum. The only olefinic proton appeared at 5.28 ppm as a multiplet. High resolution mass spectrometry registered the molecular ion at 192.1858 (calcd. for $C_{14}H_{24}$: 192.1878).

Preparation of **226** from **223** was unsuccessful. A very non-polar mixture of several compounds was produced. It was most likely that **226** was indeed formed, but was not stable under the reaction conditions. Several pathways for its decomposition could be proposed (Scheme 2-43). The most likely ones are shown below. In pathway "a", the C1-C10 σ-bond migrated as the mesylate departed. The resulting carbocation would lose one proton to give several diene compounds. In pathway "b", the π-electrons of the double bond assisted the leaving of the mesylate ion. The resulting carbocation could either lose one proton, or rearrange to open the cyclopropyl ring and then lose one proton.

By comparing the reductions of **218** and **224**, it became clear that the seven-membered acetal ring was playing a vital role in the formation of the diene **219**. Its involvement in the reaction was probably in holding the A-B rings in such a way that the angular methylene radical became close enough to the allylic 6β-hydrogen to facilitate the hydrogen abstraction. With **224**, the A-B ring system was flatter and the 6β hydrogen was out of the reach of the intermediate radical.

The formation of **219** was unexpected but was nevertheless very useful in preparing some key intermediates in the total synthesis of forskolin. The more direct linkage was with diene-lactone **72**, as appeared in Corey's synthetic scheme. From **72**, more advanced intermediates could also be prepared.

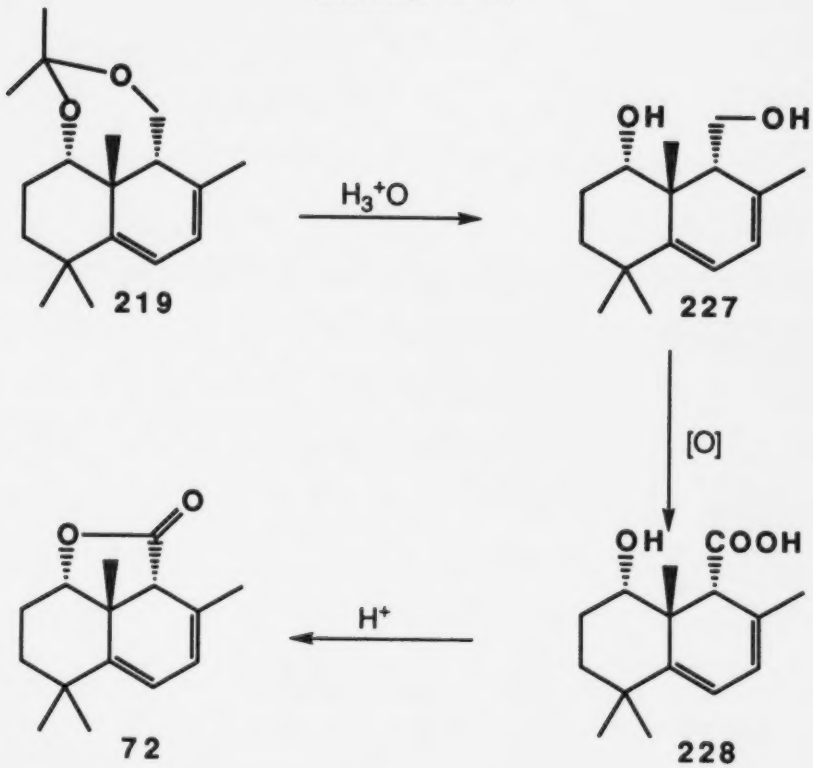
Scheme 2-43



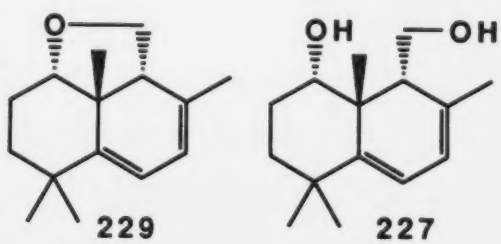
A two-step transformation of **219** to **72** was envisioned (Scheme 2-44). Removal of the acetal protecting group in acidic media followed by selective oxidation of the primary alcohol and the usually spontaneous lactonization would furnish **72**.

Considering the difficulties we had putting the acetal group on, it was natural to expect an easy removal of it. Interestingly, this was not the case. Formation of the diene turned the cup-like molecule into more or less a flat structure. Treatment of **219** with aqueous acetic acid in $CHCl_3$ or methanolic acetic acid only gave the recovered starting material. Under more vigorous

Scheme 2-44



conditions, another product, the cyclic ether **229**, was formed together with the desired diol **227** and unreacted acetal **219**. Finally, stirring the solution of **219** in a mixture of THF and 5 M H_2SO_4 (5 : 2) at room temperature for 3 hr gave 12% of the recovered starting material, 19% of cyclic ether **229** and 62% of the desired product **227**. In another run, the yield of **227** was 78% based on the initial amount of **227** and 84% based on the amount of the starting material actually consumed.



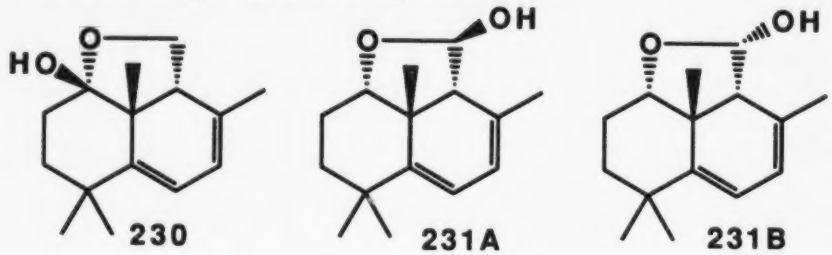
The polar compound **227**isplayed three methyl signals at 1.78, 1.15 (6 protons for two methyls) and 1.13 ppm and a broad singlet at 3.36 ppm for the two D_2O exchangeable protons of the hydroxy groups in the ^1H NMR spectrum. The two olefinic protons appeared at 5.78 and 5.58 ppm. The IR spectrum gave a broad band at 3218 cm^{-1} for the hydrogen-bonded hydroxy groups. Chemical ionization mass spectrometry registered the $M^+ + 1$ peak at m/z 237.3. The ^1H and ^{13}C NMR spectra of **229** were similar to those of **227**. But the broad band at 3218 cm^{-1} due to the hydroxy group was absent in the IR spectrum. High resolution mass spectrometry registered the molecular ion peak at 218.1667 (calcd. for $C_{15}H_{22}O$: 218.1671).

Selective oxidation of a primary alcohol in the presence of a secondary one could be effected in several ways. Caution should be exercised when choosing the oxidation reagents to avoid strong acids or double bond oxidizing agents. Strong acid would catalyze the formation of cyclic ether **229** or the addition of hydroxy groups to the diene moiety.

One method was treating **227** with Fetizon's reagent (Ag_2CO_3 on Celite) in refluxing $CHCl_3$ or benzene.[77] The primary alcohol would be oxidized at a faster rate than the secondary one to form a lactone as the major product. While the secondary alcohol was oxidized first, the minor product would be ketone-aldehyde or hemiacetal. This was a mild reagent and most functional groups would tolerate the reaction conditions. However, treating **227** with an excess of Fetizon's reagent in refluxing $CHCl_3$ or benzene did not bring about any change. The starting compound **227** was recovered.

Attempts with Jones reagent in acetone or barium permanganate in dichloromethane gave messy reaction mixtures wherein the desired product was never found. Oxidation with pyridinium chlorochromate (PCC) in dichloromethane provided the wrong product **230** in 94% yield, where the

secondary alcohol was oxidized first and a hemiacetal was formed. In this reaction, excess NaOAc was added to neutralize the hydrochloric acid and/or chromic acid that was produced during the reaction.



Compound **230** still possessed the diene moiety, as evidenced by the signal at 5.68 ppm for two olefinic protons in the ^{1}H NMR. The O-CH_2CH-C=C moiety, whose three protons appeared at 4.15, 3.45 and 2.68 ppm, suggested that the primary alcohol was neither oxidized nor cyclized to the B-ring. The disappearance of the C-1 proton, the presence of a hydroxy proton at 2.04 ppm and the high polarity of this compound indicated the presence of a hemiacetal functionality at C-1. The molecular formula was confirmed by high resolution mass spectrometry which gave the molecular ion at m/z 234.1617 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

Tris(triphenylphosphine)ruthenium(II) chloride was found by Oshima and co-workers to be able to selectively oxidize primary alcohols to aldehydes in the presence of secondary ones.[78] Treating **227** with this reagent in freshly distilled benzene at room temperature for four days provided lactol **231** in 60% yield and 9% of recovered **227** (66% yield for **231** based on the starting material actually consumed). An excess amount of this reagent oxidized **231** further into lactone **72**, but rather slowly.

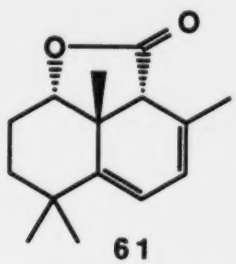
Compound **220** appeared as a single spot on t.l.c. plate. In acetone-d_6 or in a freshly prepared $CDCl_3$ solution, only one set each of ^{1}H signals and

^{13}C signals was observed in the ^{1}H and ^{13}C NMR spectra. Upon standing in $CDCl_3$ at room temperature, another set of ^{1}H or ^{13}C signals of almost equal intensity appeared, which resembled the first set closely. This was attributed to the epimerization at the lactol carbon. Before isomerization, the two olefinic protons appeared at 5.73 ppm. The α-proton of the lactol appeared at 5.09 ppm as a doublet of doublets, with couplings to the allylic proton at C-9 (6.2 Hz) and the hydroxy proton (5.2 Hz). The D_2O exchangeable hydroxy proton gave a sharp doublet at 2.84 ppm due to coupling with the lactol α-proton. The proton at C-1 moved to 4.26 ppm from 3.86 ppm as in diol **216**, due to lactol formation. In the ^{13}C NMR spectrum, the four double bond carbons and the lactol carbon appeared at 145.73, 132.73, 119.38, 118.07 and 104.52 ppm. The hydroxy group gave rise to a strong and broad IR band at 3387 cm^{-1}. High resolution mass spectrometry gave the molecular ion at 234.1620 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

The ^{1}H NMR spectrum of the other epimer displayed signals at 5.92 and 5.78 ppm for the olefinic protons, 5.25 ppm for the lactol α-proton and 2.81 ppm for the hydroxy proton. Beside the ^{13}C resonance signals at 104.52 and 63.19 ppm, two new ones appeared at 104.42 and 63.10 ppm after epimerization. These were assigned to the carbon at the epimeric center of the lactol and the allylic carbon next to it. NOE experiments did not give exclusive proof of the stereochemistry of the two epimers. When the allylic proton at C-9 was irradiated, no correlation with the α-proton of the lactol was observed in either isomer. However, a 20% increase in intensity of the hydroxy proton was observed for the second isomer. Thus, it was tentatively assigned as **231A**. The initial isomer before epimerization was therefore assigned as **231B**.

Further oxidation of **231** into **72** was very straightforward. Oxidation with Jones reagent furnished the desired lactone. The reaction looked clean on the

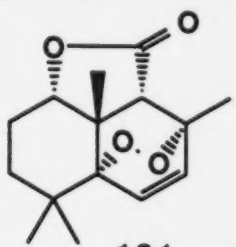
t.l.c. plate. However, the yield was only 38%. This reaction needed to be repeated and its conditions optimized. Lack of material prevented further elaboration on this reaction.



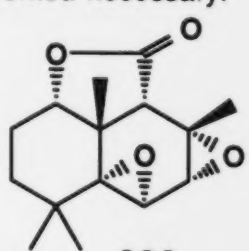
61

The IR spectrum of **72** gave a strong band at 1771 cm^{-1}, indicating the formation of the five-membered lactone ring. This was also proved by the presence of the carbonyl carbon at 176.49 ppm in the ^{13}C NMR spectrum. In the ^{1}H NMR spectrum, the olefinic protons resonated at 5.86 and 5.81 ppm. The α- proton of the lactone appeared at 2.63 ppm as a singlet. High resolution mass spectrometry registered the molecular ion peak at 232.1457 (calcd. for $C_{15}H_{20}O_2$ 232.1463).

Since Corey did not report the spectral data of **72**, further transformation of **72** into the endoperoxide **131** was deemed necessary.



131

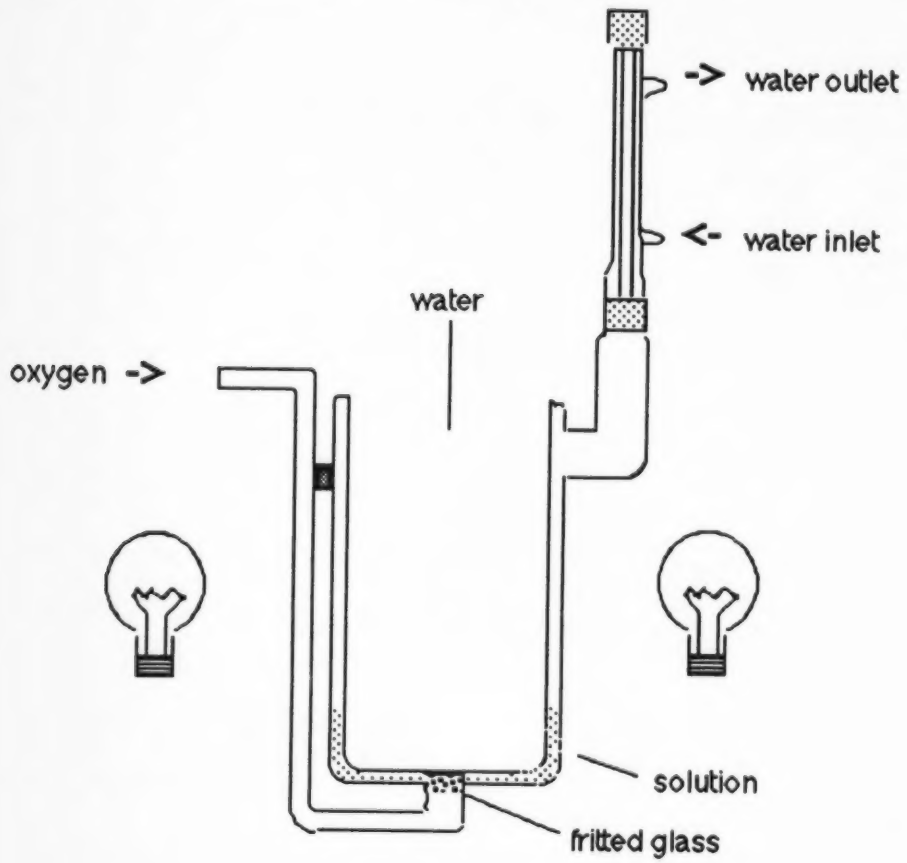


232

Corey *et al.* ran the methylene blue sensitized cycloaddition of singlet oxygen in $CHCl_3$ at 0 °C with tungsten lamps. We decide to execute it with a simpler apparatus which used running water for cooling (Figure 2-3). The

temperature was maintained at below 8 °C, even in the presence of two 200-W tungsten lights beside the reaction vessel (Figure. 2-3). Oxygen gas was introduced into the solution *via* a fritted glass as fine bubbles. A condenser was attached to minimize the loss of solvent, but it was still necessary to add more solvent to make up for the loss once a day.

Figure. 2-3 Apparatus used for singlet oxygen photoaddtion



Due to the limited amount of compound **72** and thus its low concentration, close to 0.5 equivalent of methylene blue was used. The reaction was stopped after 30 hours and **131** was isolated in 95% yield. It was

interesting to find that, when a lower concentration of methylene blue was used at this temperature and hence longer period of irradiation was required, product **131** was isomerized under this reaction condition to afford a diepoxide **232** in 27% yield, together with 30% of desired product **131**.

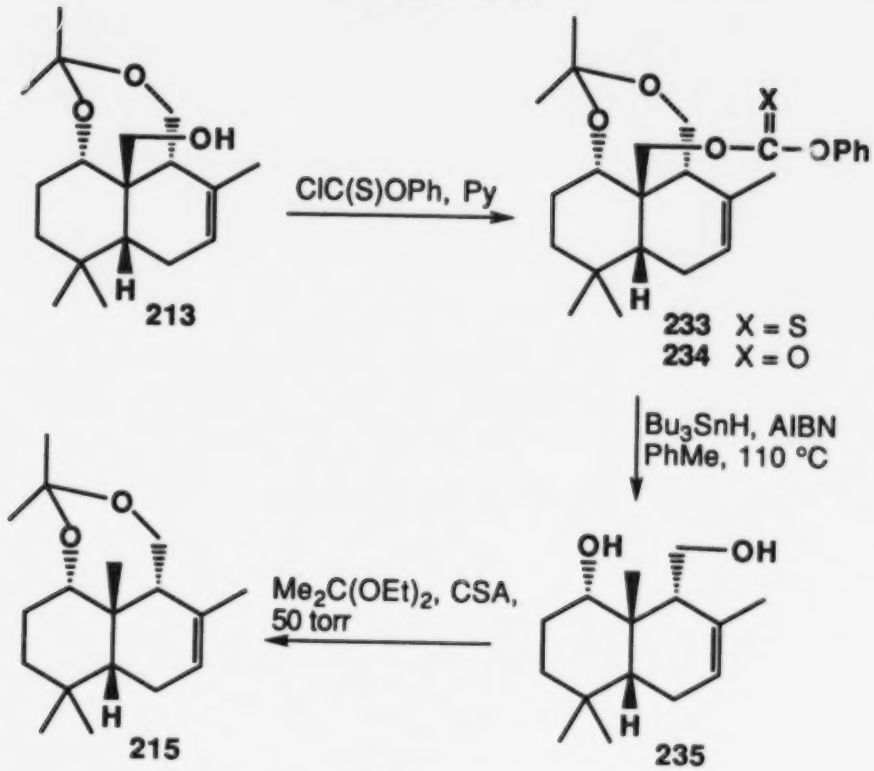
Compound **131** had identical spectral properties with those reported by Corey *et al.*. The two olefinic protons appeared at 6.68 and 6.45 ppm as two doublets in the ^{1}H NMR spectrum. The α-proton of the lactone ester oxygen at C-1 resonated at 4.37 ppm as a pseudo triplet. The α-proton of the lactone carbonyl appeared at 2.15 ppm as a singlet. The IR spectrum displayed a strong band for the lactone carbonyl at 1765 cm^{-1}. High resolution mass spectrometry gave the molecular ion peak at 264.1361 (calcd. for $C_{15}H_{20}O_4$: 264.1362).

For compound **232**, the two protons on the epoxide rings appeared in the ^{1}H NMR spectrum at 3.41 and 3.15 ppm as two doublets. The α-proton of the ester oxygen appeared at 4.22 ppm as a pseudo triplet. The IR spectrum displayed a strong carbonyl absorption at 1781 cm^{-1}. High resolution mass spectrometry registered the molecular ion at 264.1358 (calcd. for $C_{15}H_{20}O_4$: 264.1362).

Therefore, the key intermediate **72** used in Corey's scheme was prepared using our intermolecular approach in 11 steps with an overall yield of 10%. Compound **72** could also be transformed into advanced Ziegler intermediates **69** and **112**. We strongly believe there is room for improvement in the yields of the lactol and lactone formation steps.

At this point, we were prepared to continue our synthesis towards Nicolaou's intermediate **156**. Deoxygenation of the neopentyl primary alcohol could be effected in several other ways. Barton's xanthate method could be applied here (Scheme 2-45).[79]

Scheme 2-45

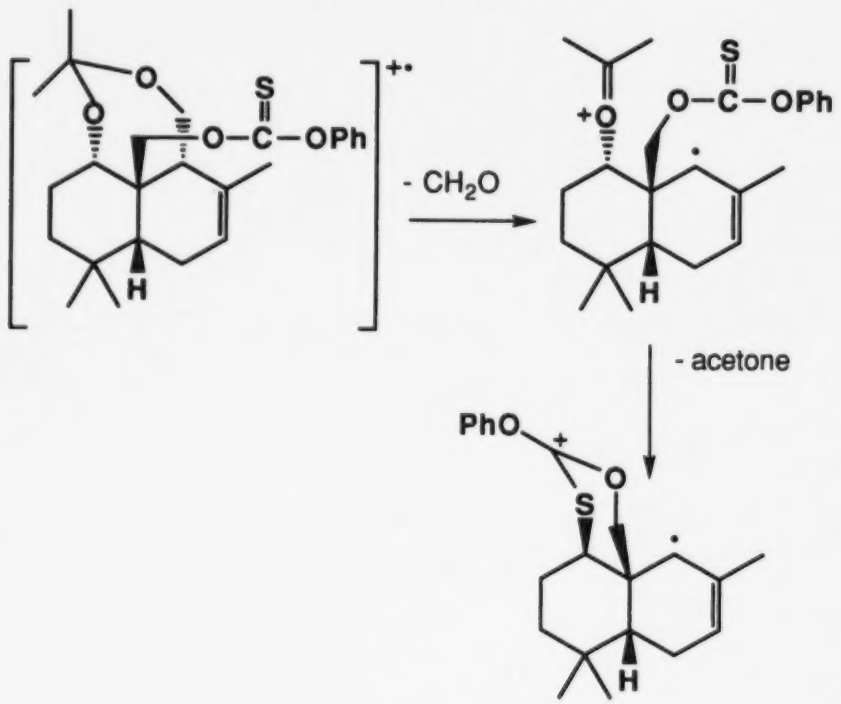


Treating **213** in a test run with phenyl chlorothionoformate and pyridine in THF at room temperature provided the desired thiocarbonate **233** in 43% yield, together with 8% of the oxygen analog **234** and 20% of the starting alcohol **213**.

The ^{1}H NMR spectrum of **233** displayed the aromatic proton resonance signals of the phenyl group at 7.47, 7.32 and 7.18 ppm. The two protons of the methylene group α to the thiocarbonate appeared at 4.26 and 4.19 ppm as two doublets. The IR spectrum gave no characteristic band for the C=S, since it appeared together with the C-O stretching bands at 1218 and 1198 cm^{-1}. High resolution mass spectrometry failed to register the molecular ion peak or the M$^+$ -CH_2O peak. There was a peak at 354.1663, likely due to the loss of an acetone molecule from the M$^+$ - CH_2O fragment (Scheme 2-46). The loss of an

acetone molecule might be assisted by the thiocarbonyl group, which would result in the formation of a membered ring and a stablized carbocation.

Scheme 2-46



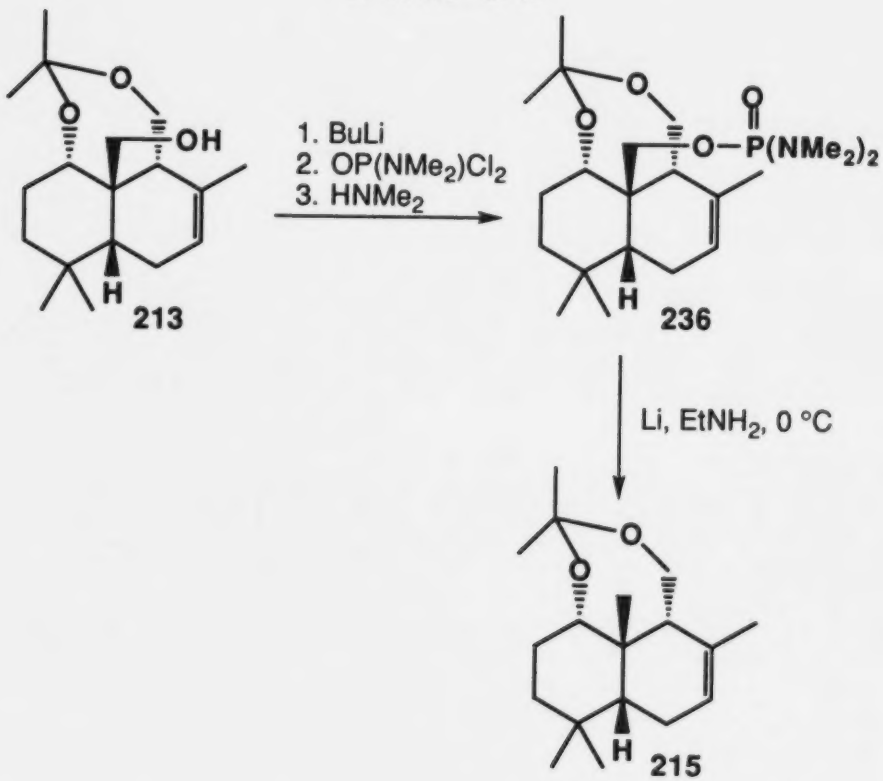
The carbonate **234** had similar spectral data. In the ^1H NMR spectrum, the aromatic protons of the phenyl group resonated at 7.43, 7.29 and 7.21 ppm. The methylene group α to the carbonate group appeared at 4.00 and 3.86 ppm as two doublets. The IR spectrum gave a strong band at 1762 cm^{-1} for the carbonate carbonyl. High resolution mass spectrometry failed to register the molecular ion peak, however, the characteristic M^+ - CH_2O peak appeared at 384.2299 (calcd. for $C_{24}H_{32}O_4$: 384.2301).

Compound **233** was treated with tributyltin hydride and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) in refluxing toluene for one day. A very polar compound resulted together with some other minor products. This

polar compound was subjected to the acetalization reaction with 2,2-diethoxypropane and CSA under vacuum (50 torr). Only 20% of the desired product **215** was isolated. Obviously, the acetal group was not stable at high temperature and/or to the reagents or the impurities in the reagents.

Another effort was made to reduce the angular hydroxymethyl group to a methyl group using the methodology developed in our group (Scheme 2-47).[80] The hindered angular neopentyl primary alcohol was deprotonated, treated with *N,N*-dimethylamidophosphorodichloridate and finally with dimethylamine in a one-pot procedure to give a *N,N,N',N'*-tetramethylphosphorodiamidate (TMPDA) **236** in 100% yield.

Scheme 2-47



Compound **236** demonstrated the typical ^{1}H and ^{13}C spectra of a TMPDA derivative. In the ^{1}H NMR spectrum, the two dimethylamido groups gave rise to two doublets with J = 9.9 Hz each at 2.63 and 2.61 ppm because of the coupling with the phosphorus atom. The two methylene protons α to the TMPDA grooup appeared as two sets of doublet of doublets, due to the geminal coupling between themselves and the coupling with the phosphorous atom. The presence of the acetal group was evidenced by a total of five singlets between 1.8 and 0.8 ppm for the methyl groups. In the ^{13}C NMR spectrum, the resonance signals for the *N*-methyls, the carbon bearing the TMPDA group and the quaternary carbon at the ring junction (C-10) were all split into doublets due to couplings to the phosphorus atom. The IR spectrum gave the P=O and C-O stretching bands at 1220 and 1075 cm^{-1}. High resolution mass spectrometry registered the molecular ion peak at 428.2800 (calcd. for $C_{22}H_{41}N_2O_4P$ 428.2804).

Reduction of **236** with lithium metal in liquid ethylamine at 0°C was straightforward despite the difficulties in handling the metal and the volatile ethylamine on a small scale.[81] Compound **215** was produced in 85% yield. No diene was produced probably due to the readily available electrons in the solution for the second electron transfer. In the ^{1}H NMR spectrum, six singlets for the methyl groups appeared at 1.70, 1.28, 1.20, 1.13, 0.99 and 0.98 ppm. The acetal group was unaffected. Only one olefinic proton appeared at 5.68 ppm as a multiplet. High resolution mass spectrometry failed to register the molecular ion peak, but gave a peak at 248.2131 for the M^{+} - CH_2O fragment (calcd. for $C_{17}H_{28}O$: 248.2140).

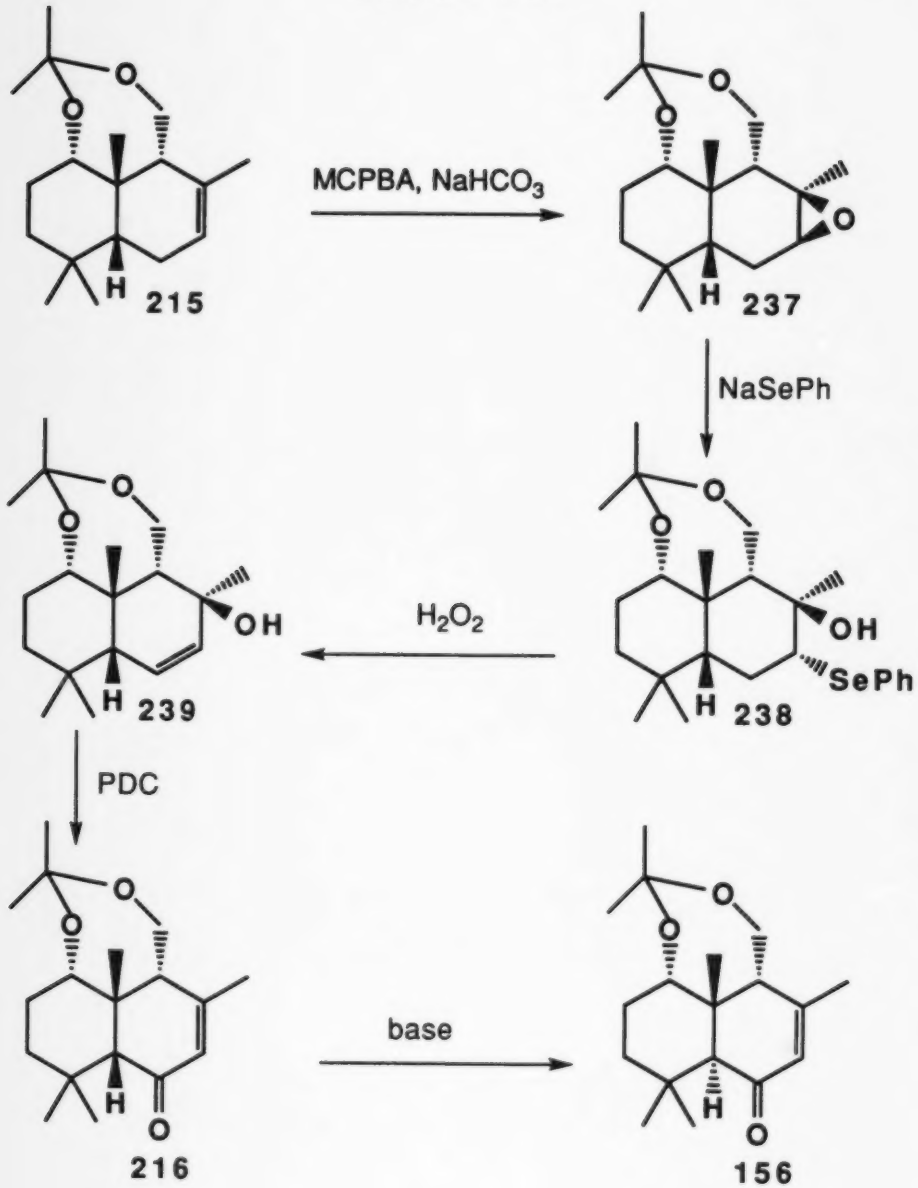
Our synthetic scheme called for the introduction of oxygen at the allylic position C-6. However, attempts for direct introduction always led to failure. A combination of chromium pentacarbonyl $Cr(CO)_6$ and *t*-BuOOH[82,83] with

compound **215** in refluxing CH_3CN gave the starting material back. Oxidation with CrO_3 and *t*-BuOOH in CH_2Cl_2[84] at room temperature, or CrO_3 and 3,5-dimethylpyrazole in CH_2Cl_2[85] at -20 °C gave complex reaction mixtures.

Indirect oxygenation at C-6 was then pursued. A five step sequence was envisioned in place of the two oxidation and epimerization steps of the direct oxygenation strategy (Scheme 2-48). Epoxidation of the double bond under neutral or slightly basic conditions would provide **237**. Controlling the pH was deemed necessary because of the presence of the acid sensitive acetal group. The addition of the epoxy ring to the existing highly strained tricyclic system also suggested the high probability of epoxy-ketone rearrangement in the presence of acid. Ring opening with phenylselenide followed by oxidative elimination would provide the allylic alcohol **239**. Oxidation of the allylic tertiary alcohol would give the desired enone **216**. Nicolaou's intermediate **156** could be reached by epimerization of **216** under basic conditions.

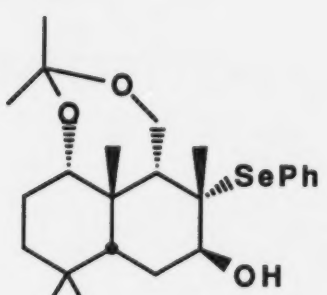
Epoxidation of **215** with MCPBA in the presence of $NaHCO_3$ at room temperature provided the desired epoxide **237** in 89% yield. The ^1H NMR spectrum of compound **237** displayed a doublet at 3.06 ppm for the α proton of the epoxide and a multiplet at 3.78 ppm for the three protons α to the oxygen atoms of the acetal ring. A total of six rmethyl signals were present which suggested the acetal ring remained intact. High resolution mass spectrometry gave the $M^+ - CH_2O$ peak at 264.2078 (calcd. for $C_{17}H_{28}O_2$: 264.2089). Chemical ionization mass spectrometry gave the $M^+ + 1 - CH_2O$ ion peak at 265.3.

Scheme 2-48



Sodium phenylselenide was prepared *in situ* by reducing diphenyl diselenide with sodium borohydride in ethanol.[86,87] A solution of **237** in an equal volume of ethanol was introduced and the reaction mixture was heated under reflux for 60 hr. The desired product **238** was isolated in 79% yield,

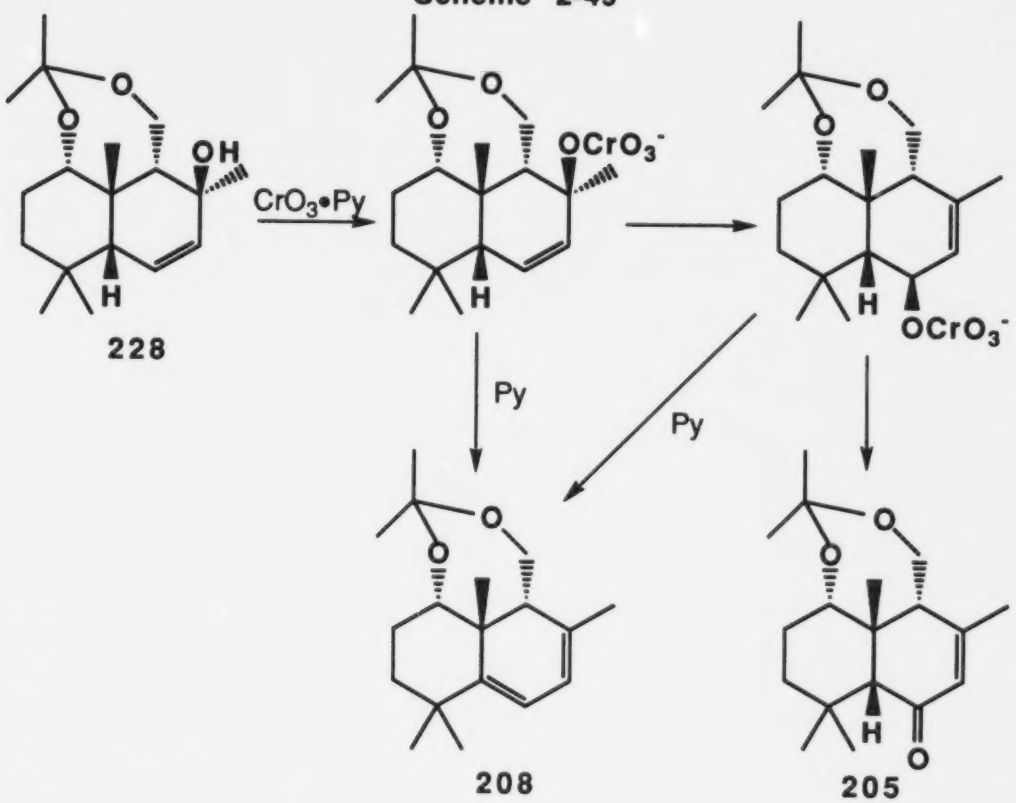
resulting from the attack of phenylselenide at the less hindered carbon of the epoxide (C-7). Attack on the more hindered carbon (C-8) gave the other isomer, compound **240**, in 6% yield. The ^{1}H NMR spectrum of **238** displayed the aromatic proton resonance signals for the phenyl group at 7.54 and 6.97 ppm as multiplets. The α-proton of the phenylselenenyl group appeared at 3.49 ppm as doublet of doublets, due to couplings with the two protons on C-6. The acetal group was intact, as evidenced by the presence of six singlets between 1.42 and 0.92 ppm for the methyl groups. High resolution mass spectrometry registered the molecular ions at 452.1861 (calcd. for $C_{24}H_{36}O_3{}^{80}Se$: 452.1830) and 450.1875 (calcd. for $C_{24}H_{36}O_3{}^{78}Se$: 450.1838). Compound **240** gave similar IR, ^{1}H, ^{13}C NMR and MS spectra. A broad band at 3320 cm^{-1} in the IR spectrum indicated the presence of a hydroxy group. The phenyl group gave rise to bands at 3070 and 1580 cm^{-1}. In the ^{1}H NMR spectrum, the phenyl group gave two multiplets at 7.61 and 7.32 ppm. The α-proton of the hydroxy group appeared at 3.55 ppm as a pseudo triplet. The presence of six singlets at 1.45, 1.40, 1.34, 1.31, 1.10, 0.74 ppm due to the methyl groups suggested the presence of the acetal group. In the ^{13}C NMR spectrum, the five resonance signals between 140 and 90 ppm indicated the presence of the phenyl and acetal groups. High resolution mass spectrometry gave the molecular peak at 452.1820 (calcd. for $C_{24}H_{36}O_3{}^{80}Se$: 452.1830).



240

Oxidative elimination with 30% hydrogen peroxide was problematic. The acetal group did not seem to be stable under these reaction conditions. A complex reaction mixture was always obtained after the addition of H_2O_2.[88]

Scheme 2-49



It is known that Jones reagent is capable of oxidizing phenylselenenylalkanes to alkenes.[89,90] Due to the presence of the acetal group in **238**, a basic medium was necessary. After the oxidative elimination, the allylic alcohol could be oxidized further into enone **216**. For this consideration, chromium trioxide in pyridine (Sarett reagent)[91] was used. Compound **238** was reacted with excess CrO_3 - pyridine at room temperature for 20 hr. The reaction turned out to be very clean. Only enone **216** and diene

219 were observed as the major products. After the removal of excess chromium reagent and pyridine, the crude product mixture was treated with 1N sodium hydroxide solution to effect the isomerization at the α position of the ketone (C-5). The desired product, enone **156**, was isolated in 49% yield. Interestingly, diene **219** was also produced. The formation of diene **219** was caused by the 1,2- and 1,4- elimination of the allylic chromates (Scheme 2-49).

Compound **156** had identical spectral properties to those reported by Nicolaou and co-workers.[48] In the IR spectrum, the carbonyl group of the enone gave a strong absorption band at 1668 cm^{-1}. In the ^1H NMR spectrum, the olefinic α-proton of the enone appeared at 5.71 ppm as a doublet. The other α-proton appeared at 2.71 ppm as a singlet. The methyl group on the β-carbon of the enone gave a doublet at 1.90 ppm. In the ^{13}C NMR spectrum, four resonance signals appeared at 199.96, 154.38, 128.50, 100.71 ppm, due to the carbonyl, the β- and the α-carbons of the enone and the acetal carbon. High resolution mass spectrometry gave the molecular ion peak at 292.2036 (calcd. for $C_{18}H_{28}O_3$: 292.2039) and the $M^+ - CH_2O$ peak at 262.1967 (calcd. for $C_{17}H_{26}O_2$: 262.1933).

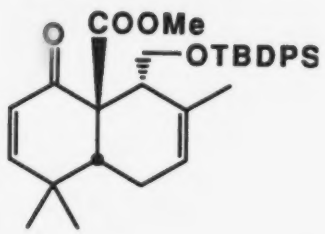
In summary, the intermolecular Diels-Alder cyclization approach utilizing dienone ester **166** and free diene alcohol **187** provided an easy and efficient way for the construction of the A-B rings of forskolin and led successfully to diene lactone **72** and endoperoxide lactone **131**, which appeared in Corey's synthetic scheme. The preparation of a more advanced intermediate **156** as appeared in Nicolaou's synthetic scheme was also accomplished *via* the indirect oxidation of **215**. It took us eleven steps from the Diels-Alder cyclization step (inclusive) to prepare compound **156** in an overall yield of 17%. This compared favorably with Nicolaou's approach, which took them 19 steps from farnesol, in an overall yield of 18%.[48]

Experimental

General and Materials

Refer to Chapter 1, Experimental for a detailed description.

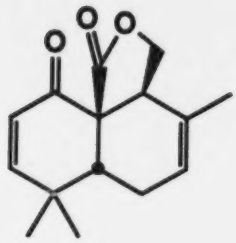
(1R*,6R*,10R*)-10-*tert*-Butyldiphenylsiloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (203)



Zinc chloride (2.00 g, 14.7 mmol) was flame-dried and melted in a round-bottomed flask under argon. It was cooled to room temperature before the addition of a solution of the *trans*-diene alcohol **187** (0.92 g, 9.4 mmol) and the diene keto ester **166** (1.35 g, 7.49 mmol) in ether (40 mL). The reaction mixture was stirred at room temperature under argon for 2 days. Water was added and the resulting mixture was extracted with ether (3 x 40 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated to afford an oily mixture. It was further concentrated at 1 torr at room temperature to remove any remaining water and the unreacted alcohol **187**. A solution of immidazole (1.9 g, 28 mmol) in DMF (20 mL) was added. The resulting reaction mixture was stirred at room temperature for 15 min before *tert*-butyldiphenylsilyl chloride (3.7 mL, 14 mmol) was added. The reaction

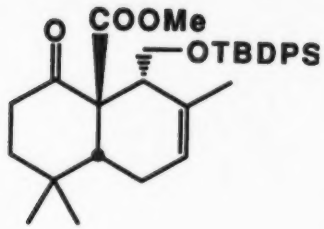
mixture was stirred at room temperature under argon for 18 hr. Absolute methanol (1 mL) was added and stirring was continued for 2 hr before water was added. The resulting mixture was extracted with ether (3 x 40 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated to afford 6.82 g of crude residue. Flash chromatography on silica gel with Skelly B and ethyl acetate (99 : 1 to 85 : 15) provided **203** (2.48 g, 4.77 mmol, 64%). Recrystallization from dichloromethane and hexanes gave white crystals: mp 143.5 - 144.5 °C; IR (KBr): 1732 (st, ester), 1691 (st, ketone, unsaturated), 1630 cm^{-1}(w, C=C conjugated); ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (m, 4H, phenyl), 7.35 (m, 6H, phenyl), 6.22 (dd, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H, C**H**=CHC=O), 5.82 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.23 (br s, 1H, C**H**=CCH_3), 4.37 (dd, J_1 = 16.5 Hz, J_2 = 8.0 Hz, 1H, OCH_2CH), 3.53 (dd, J_1 = 16.5 Hz, J_2 = 2.3 Hz, 1H, OCH_2CH), 3.33 (s, 3H, OCH_3), 2.99 (m, 1H, OCH_2C**H**), 2.61 (br t, J = *ca* 9 Hz, C**H**CH_2CH=C), 2.22 (m, 1H, CHCH_2CH=C), 1.93 (m, 1H, CHCH_2CH=C), 1.89 (s, 3H, CH=CCH_3), 1.10 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.04 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 196.18 (p), 174.57 (p), 152.98 (ap), 135.86 (ap), 135.77 (ap), 133.87 (p), 133.79 (p), 133.75 (p), 129.58 (ap), 129.49 (ap), 127.66 (ap), 127.59 (ap), 126.85 (ap), 119.68 (ap), 63.65 (p), 60.66 (p), 52.13 (ap), 50.00 (ap), 46.79 (ap), 37.67 (p), 28.22 (ap), 27.63 (ap), 27.31 (p), 26.96 (ap), 21.60 (ap), 19.20 (p); CIMS: 517 (M^+ + 1 for $C_{32}H_{40}O_4Si$). Anal. calcd. for $C_{32}H_{40}O_4Si$: C 74.38%, H 7.81%; found: C 74.68%, H 7.81%.

(1R*,5S*,9R*)-6,10,10-Trimethyl-3-oxatricyclo[7.4.0.0^{1,5}]trideca-6,11-dien-2,13-dione (204)



When a mixture of *cis*- and *trans*-3-methyl-2,4-pentadienol **187** (*Z* : *E* = 1 : 2.2) was used instead of the pure *E*-isomer, a mixture of the desired compound **203** and compound **204** were obtained in a ratio of 4.0 : 1 which were separated by flash chromatography with ethyl acetate - Skelly B (15 : 85). Recrystallization of **204** from ether - hexane gave white crystals: mp 115.5 - 116.5 °C; IR (CH_2Cl_2, cast): 1770 (st, C=O, lactone), 1673 (st, C=O, enone), 1610 cm^{-1} (w, C=C, enone); ^1H NMR (360 MHz, CDCl3): δ 6.52 (dd, J_1 = 10.0 Hz, J_2 = 1.9 Hz, 1H, C**H**=CH-C=O), 5.80 (d, J = 10.0 Hz, 1H, CH=C**H**-C=O), 5.19 (m, 1H, C**H**=CCH_3), 4.84 (dd, J_1 = 12.0 Hz, J_2 = 7.5 Hz, 1H, OC**H**$_2$CH), 4.29 (dd, J_1 = 8.0 Hz, J_2 = 7.5 Hz, 1H, OC**H**$_2$CH), 3.24 (m, 1H, OCH_2C**H**), 2.39 (m ,1H, C**H**CH_2CH=C), 2.35 (m, 1H, CHC**H**$_2$CH=C), 2.08 (m, 1H, C**H**CH_2CH=C), 1.75 (m, 3H, CH=CCH_3), 1.71 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 193.85 (p), 172.71 (p), 157.20 (ap), 130.12 (p), 124.83 (ap), 120.59 (ap), 69.25 (p), 59.05 (p), 47.76 (ap), 45.66 (ap), 37.67 (p), 30.56 (p), 30.19 (ap), 27.63 (ap), 18.83 (ap); HRMS M^+: 246.1259 (calcd. for $C_{15}H_{18}O_3$: 246.1256). Anal. calcd. for $C_{15}H_{18}O_3$: C 73.13%, H 7.37%; found: C 73.07%, H 7.44%.

(1R*,6R*,10R*)-10-*tert*-Butyldiphenylsiloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-one (209)



Reduction of **203** with the hexamer of (triphenylphosphine)copper hydride:

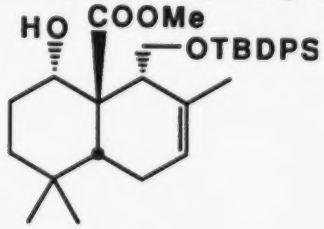
Compound **203** (0.155 g, 0.300 mmol) in benzene (3 mL) and 20 μL of water were added to the hexamer of (triphenylphosphine)copper hydride, $(Ph_3PCuH)_6$, (0.48 g, 0.24 mmol). The reaction mixture was stirred at room temperature under argon for 4 days and then exposed to the atmosphere and stirred for another 20 min. The mixture was filtered through a short column of silica gel, elution with ether - Skelly B. The filtrate was concentrated. The residue was subjected to flash chromatography with ethyl acetate - Skelly B (4 : 96) to afford **209** (155 mg, 0.298 mmol, 99%) and the recovered starting material **203** (0.85 mg, 0.5%). Compound **209** was recrystallized from ether - Skelly B to give white crystals: mp 141.5 - 142.5 °C; IR (KBr): 1721 cm^{-1} (st, C=O of the ketone and the ester); ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (m, 4H, phenyl), 7.40 (m, 6H, phenyl), 5.34 (br s, 1H, C**H**=CCH_3), 4.26 (dd, J_1 = 11.0 Hz, J_2 = 8.0 Hz, 1H, OC**H**$_2$CH), 3.49 (dd, J_1 = 11.0 Hz, J_2 = 2.0 Hz, 1H, OC**H**$_2$CH), 3.39 (s, 3H, OCH_3), 2.82 (ddd, J_1 = 16.0 Hz, J_2 = 11.5 Hz, J_3 = 7.3 Hz, 1H, C(O)C**H**$_2$CH_2), 2.75 (m, 1H, OCH_2C**H**), 2.59 (pseudo t, J = 8.5 Hz, 1H, C**H**CH_2CH=C), 2.21 (m, 1H, CHC**H**$_2$CH=C), 2.15 (m, 1H, C(O)C**H**$_2$CH_2), 1.93 (s, 3H, CH=CC**H**$_3$), 1.84 (m, 2H, CHC**H**$_2$CH=C and C(O)CH_2C**H**$_2$), 1.55 (m, 1H, C(O)CH_2C**H**$_2$), 1.12 (s, 3H, CH_3), 1.05 (s, 9H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C NMR APT (125 MHz, $CDCl_3$): δ 208.23 (p), 174.69 (p), 135.77 (ap), 135.73 (ap), 134.78 (p), 133.78 (p, two carbons, which appeared at 134.23 and 134.07 ppm in C_6D_6), 129.58 (ap), 129.51 (ap), 127.64 (ap), 127.60 (ap), 119.63 (ap), 63.59

(p), 63.02 (p), 52.12 (ap), 49.80 (ap), 49.38 (ap), 37.21 (p), 35.84 (p), 34.15 (p), 28.36 (ap), 27.66 (ap), 26.95 (ap), 25.40 (p), 21.51 (ap), 19.21 (p); HRMS: 461.2151 (M^+ - *t*-Bu, calcd. for $C_{28}H_{33}O_4Si$: 461.2148); CIMS: 519.2 (M^+ + 1). Anal. calcd. for $C_{32}H_{42}O_4Si$: C 74.09%, H 8.17; found: C 74.36%, H 8.27%.

Reduction of **203** with tetrakis(triphenylphosphine)palladium(0) - zinc chloride - diphenylsilane:

Compound **203** (49.5 mg, 0.096 mmol), diphenylsilane (112 mg, 0.61 mmol), tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol), zinc chloride (49.30 mg, 0.36 mmol), water (3 μl, 0.17 mmol) and chloroform (1 mL; neutralized by passing through a column of neutral alumna) were mixed together. The reaction mixture was stirred at room temperature under argon for 27 hr, and then passed through a short, thin column of silica gel, eluting with ether - Skelly B. The eluate was concentrated and the residue was subjected to flash chromatography. Elution with ethyl acetate - Skelly B (3 : 97 to 5 : 95) afforded **209** (37.4 mg, 0.072 mmol, 60%, 80% based the starting material consumed) and the recovered starting material **204** (12.10 mg, 24%).

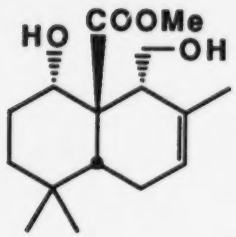
(1R*,2S*,6R*,10R*)-10-*tert*-Butyldiphenylsiloxymethyl-1-carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (210)



Lithium tri-*tert*-butoxyaluminohydride (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added to a solution of **209** (0.573 g, 1.10 mmol) in THF (10 mL)

under argon. The reaction mixture was stirred at room temperature under argon for 36 hr and then slowly poured into ice-cold 1N HCl (15 mL). The resulting mixture was extracted with ether (3 x 20 mL). The extracts were washed sequentially with water, saturated sodium bicarbonate solution and saturated sodium chloride solution, dried, filtered and concentrated. The crude product was subjected to flash chromatography. Elution with ethyl acetate - Skelly B (2.5 : 97.5 to 10 : 90) afforded **210** (0.564 g, 1.08 mmol, 98%). Recrystallization from ether - hexane gave white crystals: mp 168.0 - 169.0 °C; IR (CH_2Cl_2, cast): 3510 (br, md, hydroxyl), 1720 cm^{-1} (st, C=O of the ester); ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 4H, phenyl), 7.42 (m, 6H, phenyl), 5.64 (br s 1H, $CH{=}CCH_3$), 4.60 (br s, 1H, $HOCHCH_2CH_2$), 3.88 (d, J = 11.1 Hz, 1H, OCH_2CH), 3.77 (br s, 1H, D_2O exchangeable, -OH), 3.75 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, OCH_2CH), 3.54 (s, 3H, OCH_3), 2.50 (br s, 2H), 2.25 - 1.65 (m, 5H), 1.53 (br s, $CH{=}CCH_3$), 1.10 (s, 9H, $C(CH_3)_3$), 0.98 (m, 1H), 0.91 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C NMR APT (100 MHz, $CDCl_3$): 178.22 (p), 136.04 (ap), 135.94 (ap), 132.34 (p), 132.25 (p), 129.97 (ap), 129.94 (ap), 129.57 (p), 127.73 (ap), 127.66 (ap), 126.07 (ap), 68.12 (ap), 61.02 (p), 51.87 (p), 51.23 (ap), 49.01 (ap), 42.47 (ap), 34.18 (p), 30.70 (ap), 28.64 (p), 27.37 (ap), 27.00 (ap), 26.78 (p), 26.50 (p), 21.21 (ap), 19.19 (p); HRMS M^+: 520.3013 (calcd. for $C_{32}H_{44}O_4Si$: 520.3009). Anal. calcd. for $C_{32}H_{44}O_4Si$: C 73.80%, H 8.52%; found: C 73.45%, H 8.75%.

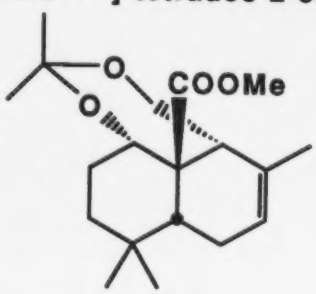
(1R*,2S*,6R*,10R*)-1-Carbomethoxy-10-hydroxymethyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-en-2-ol (211)



Tetrabutylammonium fluoride (TBAF, 1M solution in THF, 10 mL, 10 mmol) was added to a solution of **210** (2.59 g, 4.99 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 1.5 hr. Water (50 mL) was added and the resulting mixture was extracted with ether (3 x 50 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with acetone- Skelly B (1 : 5) gave **211** (1.406 g, 4.98 mmol, 100%). Recrystallization from dichloromethane - ether - hexane gave white, needle-like crystals: mp 149.5 - 150.0 °C; IR (KBr): 3257 (st, br, hydrogen-bonded hydroxyls), 1716 (st, C=O of the ester), 1217 (st, C-O of the ester), 1047 (st, C-O of the alcohols), 1020 cm^{-1} (st, C-O of the alcohols); ^1H NMR (400 MHz, $CDCl_3$): δ 5.64 (br s, 1H, C**H**=CCH_3), 4.53 (br s, 1H, HOC**H**CH_2CH_2), 3.96 (dd, J_1 = 11.4 Hz, J_2 = 4.5 Hz, 1H, HOC**H**$_2$CH), 3.85 (br d, J = 11.4 Hz, 1H, HOC**H**$_2$CH), 3.62 (s, 3H, OCH_3), 2.90 (br s, 2H, D_2O exchangeable, -OHs), 2.60 (br s, 1H, OCH_2C**H**), 2.43 (m, 1H, CHC**H**$_2$CH=C), 2.19 (dd, J_1 = 11.3 Hz, J_2 = 6.0 Hz, 1H, C**H**CH_2CH=C), 2.07 (m, 2H, OCHC**H**$_2$CH_2 and CHC**H**$_2$CH=C), 1.87 (ddd, J_1 = 14.0 Hz, J_2 = 14.0 Hz, J_3 = 3.0 Hz, OCHCH_2C**H**$_2$), 1.81 (br s, 3H, CH=CC**H**$_3$), 1.70 (ddd, J_1 = 14.5 Hz, J_2 = 6.2 Hz, J_3 = 3.0 Hz, 1H, OCHC**H**$_2$CH_2), 0.97 (br d, J =14.0 Hz, 1H, OCHCH_2C**H**$_2$), 0.91 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C NMR APT (100 MHz, $CDCl_3$): 178.42 (p), 130.09 (p), 125.48 (ap), 68.34 (ap), 58.88 (p), 51.41 (ap), 48.33 (p), 42.29 (ap), 34.15 (p), 30.68 (ap), 28.50 (two carbons,

p), 27.33 (ap), 26.79 (p), 26.52 (p), 21.38 (ap); HRMS M^+: 282.1824 (calcd. for $C_{16}H_{26}O_4$: 282.1831). Anal. calcd. for $C_{16}H_{26}O_4$: C 68.04%, H 9.29%; found: C 68.11%, H 9.46%.

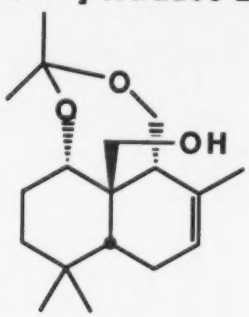
(1R*,5R*,9S*,14R*)-14-Carbomethoxy-2,6,6,11,11-pentamethyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]-tetradec-2-ene (212)



Compound **211** (0.767 g, 2.72 mmol) and camphorsulfonic acid (CSA, 88 mg, 0.38 mmol) were dissolved in 2,2-diethoxypropane (8 mL, 50 mmol) and the reaction mixture was stirred at room temperature under reduced pressure (55 torr) for 9 hr. Saturated sodium bicarbonate solution (5 mL) was added to neutralize camphorsulfonic acid and the resulting mixture was extracted with ether (3 x 40 mL). The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with acetone - Skelly B (5 : 95 to 10 : 90) afforded **212** (0.859 g, 2.67 mmol, 98%): IR ($CDCl_3$, cast): 1718 cm^{-1} (st, C=O of the ester group); ^1H NMR (200 MHz, $CDCl_3$): δ 5.68 (br d, J = 6.0 Hz, 1H, C**H**=CCH_3), 4.85 (m, 1H, OC**H**CH_2), 4.04 (br d, J = 13.9 Hz, 1H, O**CH$_2$**CH), 3.80 (dd, J_1 = 13.9 Hz, J_2 = 5.0 Hz, 1H, O**CH$_2$**CH), 3.63 (s, 3H, OCH_3), 2.28 (m, 1H), 2.00 (m, 3H), 1.72 (br s, 3H, CH=C**CH$_3$**), 1.71 (m, 1H), 1.50 (m, 1H), 1.42 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.93 (m, 1H), 0.92 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR APT (100 MHz,

$CDCl_3$): δ 178.79 (p), 131.37 (p), 124.45 (ap), 100.19 (p), 69.19 (ap), 60.35 (p), 51.52 (ap), 51.40 (p), 50.88 (ap), 43.45 (ap), 33.67 (p), 30.94 (ap), 29.95 (ap), 28.81 (p), 27.18 (ap), 26.84 (p), 24.51 (p), 21.84 (ap), 20.41 (ap); HRMS: 307.1909 (M^+ - Me, calcd. for $C_{18}H_{27}O_4$: 307.1910), 292.2028 (M^+ - CH_2O, calcd. for $C_{18}H_{28}O_3$: 292.2039).

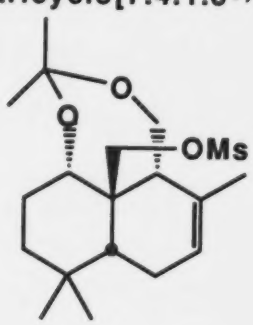
(1R*,5R*,9S*,14R*)-14-Hydroxymethyl-2,6,6,11,11-pentamethyl-10,12-dioxatricyclo[7.4.1.$0^{5,14}$]-tetradec-2-ene (213)



At 0 °C, a solution of **212** (0.355 g, 1.10 mmol) in ether (4 mL) was added to a suspension of $LiAlH_4$ (90%, 90.35 mg, 2.3 mmol) in ether (3 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 3 hr under argon. The reaction mixture was cooled to 0 °C with an ice-bath and ether (10 mL) was added. Water (2 drops), 1N NaOH solution (2 drops) and water (5 drops) were slowly added in sequence. The resulting suspension was filtered. The filtrate was dried, filtered and concentrated. The crude product was subjected to flash chromatography on silica gel which was pre-treated with triethylamine. Elution with ethyl acetate - Skelly B (15 : 85) afforded **213** (0.298 g, 1.01 mmol, 92%). It was recrystallized from ether - hexane to give white, needle-like crystals: mp 86.5 - 88.0 °C; IR (acetone-d_6, cast): 3428 (br, md, -OH), 1220 (st, C-O), 1075 (st, C-O), 1061 cm^{-1} (st, C-O); ^1H

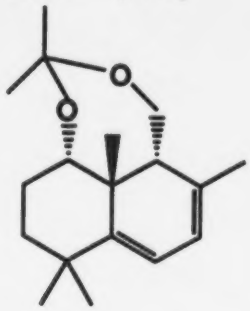
NMR (360 MHz, acetone-d_6): δ 5.68 (m, 1H, $CHCH_2CH{=}CCH_3$), 4.31 (d, J = 6.8 Hz, 1H, $OCHCH_2CH_2$), 3.96 (t, J = 5.8 Hz, 1H, D_2O exchangeable, -OH), 3.68 (dd, J_1 = 12.4 Hz, J_2 = 10.5 Hz, 1H, OCH_2CH), 3.33 (dd, J_1 = 12.4 Hz, J_2 = 4.0 Hz, 1H, OCH_2CH), 3.31 (dd, J_1 = 10.9 Hz, J_2 = 5.8 Hz, 1H, $HOCH_2C$), 2.96 (dd, J_1 = 10.9 Hz, J_2 = 5.8 Hz, 1H, $HOCH_2C$), 2.68 (dd, J_1 = 10.5 Hz, J_2 = 4.0 Hz, 1H, OCH_2CH), 2.08 (dddd, J_1 = 15.0 Hz, J_2 = 9.0 Hz, J_3 = 6.8 Hz, J_4 = 3.5 Hz, 1H, $OCHCH_2CH_2$), 1.96 (m, 2H, $CHCH_2CH{=}C$), 1.69 (br s, 3H, $CH{=}CCH_3$), 1.66 (dddd, J_1 = 15.0 Hz, $J_2 = J_3$ = 9.0 Hz, J_4 = 1.2 Hz, 1H, $OCHCH_2CH_2$), 1.50 (ddd, J_1 = 13.9 Hz, J_2 = 9.0 Hz, J_3 = 3.5 Hz, 1H, $OCHCH_2CH_2$), 1.36 (ddd, J_1 = 13.9 Hz, $J_2 = J_3$ = 9.0 Hz, 1H, $OCHCH_2CH_2$), 1.28 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.74 (dd, J_1 = 11.7 Hz, J_2 = 5.6 Hz, 1H, $CHCH_2CH{=}CCH_3$); ^{13}C NMR APT (75 MHz, acetone-d_6): δ 136.36 (p), 125.59 (ap), 100.76 (p), 70.10 (p), 68.55 (ap), 62.23 (p), 49.49 (ap), 48.37 (ap), 45.72 (p), 34.75 (p), 34.59 (ap), 32.49 (p), 26.88 (p), 26.06 (ap), 25.85 (p), 25.42 (ap), 23.84 (ap), 23.00 (ap); HRMS: 264.2086 (M^+ - CH_2O, calcd. for $C_{17}H_{28}O_2$: 264.2089); CIMS: 295.1 (M^+ + 1).

(1R*,5R*,9S*,14R*)-14-Methanesulfonyloxymethyl-2,6,6,11,11-pentamethyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]-tetradec-2-ene (218)



With stirring and cooling with an ice-bath, triethylamine (0.34 mL, 2.4 mmol) and mesyl chloride (0.15 mL, 1.9 mmol) were added in sequence to a solution of **213** (285 mg, 0.97 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 5 hr under argon and then poured into ice-cold saturated sodium bicarbonate solution. It was extracted with ether (3 x 40 mL). The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel which was pre-treated with triethylamine. Elution with ether - Skelly B (1 : 20) gave **218** (0.324 mg, 0.87 mmol, 90%). Recrystallization from ether - hexane gave white crystals: mp 106.0-107.0 °C; IR (acetone-d_6, cast): 3020 (w, olefinic C-H); 1355 (st, S=O), 1220 (st, C-O), 1177 cm^{-1} (st, S=O); ^1H NMR (360 MHz, acetone-d_6): δ 5.75 (m, 1H, C=C**H**), 4.19 (d, J = 6.6 Hz, 1H, OC**H**CH_2CH_2), 3.96 (d, J = 9.9 Hz, 1H, C**H**$_2$OMs), 3.71 (d, J = 9.9 Hz, 1H, C**H**$_2$OMs), 3.70 (dd, J_1 = 12.6 Hz, J_2 = 10.4 Hz, 1H, OC**H**$_2$CH), 3.37 (dd, J_1 = 12.6 Hz, J_2 = 4.1 Hz, 1H, OC**H**$_2$CH), 3.13 (s, 3H, OSO_2C**H**$_3$), 2.49 (dd, J_1 = 10.4 Hz, J_2 = 4.1 Hz, 1H, OC**H**$_2$CH), 2.05 (m, 3H), 1.73 (s, 3H, CH=CC**H**$_3$), 1.72 (dddd, J_1 = 15.3 Hz, $J_2 = J_3$ = 8.6 Hz, J_4 = 1.1 Hz, 1H, OCHC**H**$_2$$CH_2$), 1.56 (ddd, J_1 = 14.1 Hz, J_2 = 8.8 Hz, J_3 = 3.5 Hz, 1H, $OCHCH_2$C**H**$_2$), 1.42 (ddd, J_1 = 14.1 Hz, $J_2 = J_3$ = 9.0 Hz, 1H, $OCHCH_2$C**H**$_2$), 1.28 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.92 (dd, J_1 = 9.9 Hz, J_2 = 7.2 Hz, 1H, $CHCH_2$CH=C); ^{13}C NMR APT (100 MHz, acetone-d_6): δ 135.57 (p), 125.97 (ap), 101.07 (p), 75.81 (p), 67.74 (ap), 61.75 (p), 49.87 (ap), 47.67 (ap), 44.19 (p), 36.90 (ap), 34.30 (ap), 33.92 (p), 32.41 (p), 26.43 (p), 25.71 (ap), 25.43 (p), 25.20 (ap), 23.60 (ap), 22.62 (ap); HRMS: 342.1862 (M^+ - CH_2O, calcd. for $C_{18}H_{30}O_4S$: 342.1865); CIMS: 373.4 (M^+ + 1). Anal. calcd. for $C_{19}H_{32}O_5S$: C 61.26%, H 8.66%; found: C 61.40%, H 8.67%.

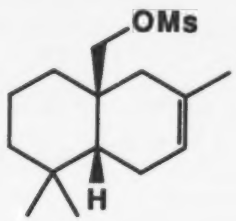
(1R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxatricyclo-[7.4.1.0^{5,14}]tetradeca-2,4-diene (219)



Compound **218** (0.296 g, 0.794 mmol), zinc powder (3.65 g, 56 mmol), sodium iodide (1.15 g, 7.7 mmol) and dry DMF (5 mL) were mixed together and the suspension was immersed in an oil bath pre-heated to 110 °C. The reaction mixture was stirred under argon for 24 hr. After cooling down to room temperature, the reaction mixture was poured into water (20 mL) and the mixture was extracted with ether (3 x 40 mL). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. Flash chromatography on silica gel with ether - Skelly B (5 : 95) gave **219** (189 mg, 0.68 mmol, 86%) as a colorless oil: IR (acetone-d_6, cast): 3070 (w, olefin C-H), 1670 (w, C=C), 1610 (w, C=C), 1221 (st, C-O), 1074 cm^{-1} (st, C-O); ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.76 (d, J = 5.7 Hz, 1H, C=C**H**-CH=C-Me), 5.58 (dq, J_1 = 5.7 Hz, J_2 = 1.5 Hz, 1H, C=CH-C**H**=C-Me), 3.82 (d, J = 4.2 Hz, 1H, OC**H**), 3.71 (dd, J_1 = 12.2 Hz, J_2 = 10.1 Hz, 1H, OC$\mathbf{H_2}$CH), 3.16 (dd, J_1 = 12.2 Hz, J_2 = 2.7 Hz, 1H, OC$\mathbf{H_2}$CH), 1.97 (m, 2H, OCHC$\mathbf{H_2}$C$\mathbf{H_2}$), 1.78 (dd, J_1 = 10.1 Hz, J_2 = 2.7 Hz, 1H, OCH$_2$C**H**), 1.74 (d, J = 1.5 Hz, 3H, C=C-C$\mathbf{H_3}$), 1.55 (m, 1H, OCHCH$_2$C$\mathbf{H_2}$), 1.32 (s, 3H, CH_3), 1.25(s, 3H, CH_3), 1.19 (m, 1H, OCHCH$_2$C$\mathbf{H_2}$), 1.16 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, acetone-d_6): δ 152.57 (p), 135.40 (p), 124.85 (ap), 123.16

(ap), 105.03 (p), 77.83 (ap), 63.58 (p), 61.15 (ap), 47.14 (p), 39.74 (ap), 38.66 (p), 38.07 (p), 36.42 (ap), 30.41 (ap), 30.10 (p), 28.71 (ap), 28.48 (ap), 26.50 (ap); HRMS: 276.2083 (M^+, calcd. for $C_{18}H_{28}O_2$: 276.2089), 246.1978 (M^+ - CH_2O, calcd. for $C_{17}H_{26}O$: 246.1978).

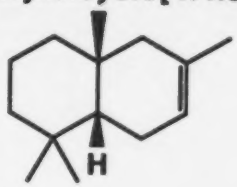
(1S*,6R*)-1-Methanesulfonyloxymethyl-3,7,7-trimethylbicyclo-[4.4.0]dec-3-ene (224)



Triethylamine (0.26 mL, 1.4 mmol) was added to a solution of **222** (154 mg, 0.74 mmol) in THF (3 mL). The mixture was cooled to 0 °C with an ice-bath before mesyl chloride (0.12 mL, 1.5 mmol) was slowly added. The reaction mixture was stirred at room temperature under argon for 2 hr. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated to afford a crude mixture (191 mg). It was then subjected to flash chromatography on silica gel. Gradient elution with ethyl acetate and Skelly B (5 : 95 to 10 : 90) gave compound **224** (212 mg, 0.74 mmol, 90%): IR ($CDCl_3$, cast): 1355 (st, S=O), 1176 cm^{-1} (st, S=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.32 (m, 1H, C**H**=CCH$_3$), 3.96 (d, J = 9.1 Hz, 1H, C**H**$_2$OMs), 3.88 (d, J = 9.1 Hz, 1H, C**H**$_2$OMs), 2.98 (s, 3H, OSO_2CH_3), 2.27 (br d, J = 8.8 Hz, 1H), 2.11 (br s, 1H), 1.62 (s, 3H, CH=CC**H**$_3$), 1.58 - 1.38 (m, 6H), 1.33 (m, 1H), 1.21 (ddd, $J_1 = J_2 = 12.0$ Hz, $J_3 = 3.4$ Hz, 1H), 0.91 (s, 3H, CH_3), 0.81 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 131.01 (p), 120.04

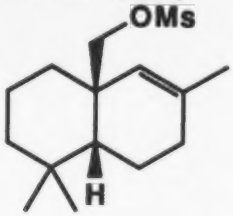
(ap), 41.96 (p), 40.94 (ap), 36.97 (ap), 36.65 (p), 34.44 (p), 33.89 (p), 33.78 (p), 33.34 (ap), 23.57 (ap), 23.31 (p), 21.68 (ap), 18.05 (p); HRMS M^+: 286.1599 (calcd. for $C_{15}H_{26}O_3S$: 286.1603).

(1R*,6R*)-1,3,7,7-Tetramethylbicyclo[4.4.0]dec-3-ene (225).



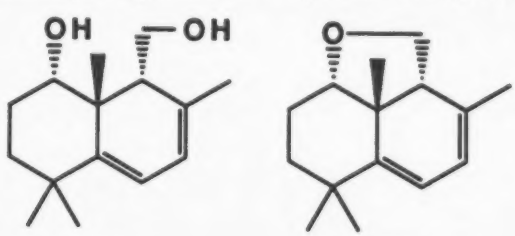
A mixture of **224** (161 mg, 0.564 mmol), NaI (420 mg, 2.8 mmol), zinc powder (1.83 g, 28 mmol) and dry DMF (6 mL) was heated in an oil bath at 130 °C for three days. The reaction was monitored with thin-layer chromatography. As the starting material disappeared, a compound was formed which was not visible on the chromatogram under a UV (254 nm) lamp. At room temperature, water was added and the mixture was extracted with ether. The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated to afford 112 mg of crude reaction product which was almost pure **225**. The crude product was purified by flash chromatography on silica gel. Elution with Skelly B afforded **225** (45.0 mg, 0.23 mmol, 42%): IR ($CHCl_3$, cast): 1460 (st, Me), 1365 cm^{-1} (st, Me); ^1H NMR (200 MHz, $CDCl_3$): δ 5.28 (m, 1H, $CH{=}CCH_3$), 2.30 - 1.92(m, 4H), 1.61 (br s, 3H, $CH{=}CCH_3$), 1.60 - 0.93 (m, 7H), 0.90 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.76 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 131.99 (p), 119.58 (ap), 47.25 (ap), 42.75 (p), 40.91 (p), 38.84 (p), 33.94 (p), 33.52 (ap), 32.39 (p), 32.00 (ap), 23.80 (ap), 23.57 (p), 21.33 (ap), 18.96 (p); HRMS M^+: 192.1858 (calcd. for $C_{14}H_{24}$: 192.1878).

An attempt to prepare (1R*,6R*)-1-Methanesulfonyloxymethyl-3,7,7-trimethylbicyclo[4.4.0]dec-2-ene (226)



Mesyl chloride (0.10 mL, 1.3 mmol) was slowly added to a solution of **223** (135 mg, 0.647 mmol) and triethylamine (0.23 mL, 1.6 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at room temperature under argon for 2 hr. Saturated aqueous $NaHCO_3$ solution was added at 0 °C and mixture was extracted with ether (3 x 15 mL). The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated to afford a crude mixture (155 mg) of several extremely non-polar compounds whose R_f values were almost 1 with Skelly B as the developing solvent. The ^1H NMR spectrum indicated the absence of any proton α to oxygen, chlorine, or any proton on a cyclopropyl ring. Several resonance signals for olefinic protons at around 6 ppm indicated the presence of several olefins.

(1R*,2S*,10R*)-10-Hydroxymethyl-1,5,5,9-tetramethylbicyclo[4.4.0]-deca-6,8-dien-2-ol (216) and (5R*,8S*,12R*)-4,11,11,12-tetramethyl-7-oxatricyclo[6.3.1.0^{5,12}]dodeca-1,3-diene (218)

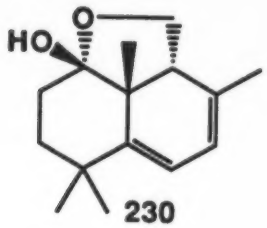


228 230

To a solution of **219** (12.05 mg, 0.0436 mmol) in THF (1 mL) was added 1N HCl solution (0.5 mL). The reaction mixture was stirred at room temperature for 1 hr. Thin-layer chromatography indicated that the reaction was slow. Concentrated sulfuric acid (5 drops) was added at 0 °C. The resulting solution was stirred at room temperature for 5 hr. Saturated $NaHCO_3$ solution was added dropwise and the neutralized reaction mixture was extracted with ether. The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography on silica gel with ether - Skelly B (1 : 20) gave the recovered starting material (0.97 mg, 8%). Further elution with acetone - Skelly B (1 : 6) gave compound **227** (7.99 mg, 0.0339 mmol, 78%, 84% based the starting material consumed). In another run on a larger scale, a solution of **219** (143 mg, 0.518 mmol) in THF (5 mL) was mixed with 5M H_2SO_4 (2 mL) at 0 °C and the resulting reaction mixture was stirred at room temperature for 3 hr. Saturated $NaHCO_3$ solution was slowly added at 0°C until the bubbling ceased. The resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with ether - Skelly B (1 : 20) gave the recovered starting material (17.68 mg, 12%) and **229** (21.38 mg, 0.098 mmol, 19%, 22% based on the starting material consumed). Further elution with acetone - Skelly B (1 : 6) gave **227** (76.63 mg, 0.32 mmol, 62%, 71% based on the starting material consumed). Compound **227**: mp 126.5 - 128.0 °C; IR (CH_2Cl_2, cast): 3218 (br, st, hydrogen-bonded hydroxyls), 1060 (st, C-O), 1045 cm^{-1} (st, C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.78 (d, J = 5.6 Hz, 1H, =C**H**-CH=CCH_3), 5.58 (dq, J_1 = 5.6 Hz, J_2 = 1.5 Hz, 1H, =CH-C**H**=CCH_3), 3.86 (dd, J_1 = 6.5 Hz, J_2 = 2.7 Hz, 1H, CH_2C**H**OH), 3.73 (dd, J_1 = 11.7 Hz, J_2 = 7.7 Hz, 1H, CHC**H**$_2$OH), 3.40 (dd, J_1 = 11.7 Hz, J_2 = 1.8 Hz, 1H, CHC**H**$_2$OH), 3.36 (br s,

2H, D_2O exchangeable, OHs), 2.02 (dddd, J_1 = 13.1 Hz, J_2 = 10.5 Hz, J_3 = 4.9 Hz, J_4 = 2.7 Hz, 1H, $HOCHCH_2CH_2$, ax), 1.89 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H, $CHCH_2OH$), 1.80 (ddd, J_1 = 13.5 Hz, J_2 = 10.5 Hz, J_3 = 5.0 Hz, 1H, $HOCHCH_2CH_2$, ax), 1.78 (d, J = 1.5 Hz, 3H, $CH=CCH_3$), 1.70 (dddd, J_1 = 13.1 Hz, J_2 = 6.5 Hz, J_3 = 5.0 Hz, J_4 = 4.9 Hz, 1H, $HOCHCH_2CH_2$, eq), 1.35 (ddd, J_1 = 13.4 Hz, J_2 = J_3 = 4.9 Hz, $HOCHCH_2CH_2$, eq), 1.15 (s, 6H, two CH_3s), 1.13 (s, 3H, CH_3); ^{13}C NMR APT (50 MHz, $CDCl_3$): δ 147.64 (p), 133.40 (p), 119.61 (ap), 119.05 (ap), 74.66 (ap), 60.05 (p), 53.91 (p), 44.15 (p), 34.55 (ap), 34.37 (p), 33.60 (p), 31.64 (ap), 27.32 (p), 24.99 (ap), 22.25 (ap); CIMS: 236.2 (M^+), 237.3 (M^+ + 1), 254.3 (M^+ + 18). Compound **229**: IR ($CDCl_3$, cast): 1019 (st, C-O), 1050 cm^{-1} (st, C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.73 (d, J = 5.6 Hz, 1H, $C=CH-CH=CCH_3$), 5.68 (dq, J_1 = 5.6 Hz, J_2 = 1.5 Hz, 1H, $C=CH-CH=CCH_3$), 4.02 (dd, J_1 = 8.3 Hz, J_2 = 7.1 Hz, OCH_2CH), 3.92 (pseudo t, J = 3.0 Hz, 1H, $OCHCH_2CH_2$), 3.42 (dd, J_1 = 10.9 Hz, J_2 = 7.1 Hz, 1H, OCH_2CH), 2.24 (dd, J_1 = 10.9 Hz, J_2 = 8.3 Hz, 1H, OCH_2CH), 1.93 (dddd, J_1 = 14.5 Hz, J_2 = 13.3 Hz, J_3 = 3.6 Hz, J_4 = 3.0 Hz, 1H, $OCHCH_2CH_2$, ax), 1.83 (dddd, J_1 = 14.5 Hz, J_2 = 4.1 Hz, J_3 = 3.6 Hz, J_4 = 3.0 Hz, 1H, $OCHCH_2CH_2$, ax), 1.80 (d, J = 1.5 Hz, 3H, $C=CH-CH=CCH_3$), 1.55 (ddd, J_1 = J_2 = 13.3 Hz, J_3 = 4.1 Hz, 1H, $OCHCH_2CH_2$, ax), 1.23 (ddd, J_1 = 13.3 Hz, J_2 = J_3 = 3.6 Hz, 1H, $OCHCH_2CH_2$, eq), 1.12 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 144.45 (p), 131.78 (p), 119.01 (ap), 116.94 (ap), 86.13 (ap), 71.28 (p), 54.74 (ap), 43.45 (p), 34.84 (p), 33.89 (p), 30.76 (ap), 28.71 (ap), 23.41 (p), 23.12 (ap), 22.37 (ap); HRMS M^+: 218.1667 (calcd. for $C_{15}H_{22}O$: 218.1671).

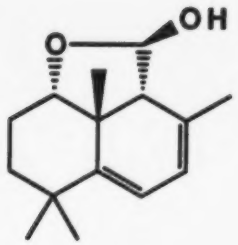
(1S*,4R*,12R*)-5,9,9,12-Tetramethyl-2-oxatricyclo[6.3.1.0^{4,12}]-dodeca-5,7-dien-1-ol (230)



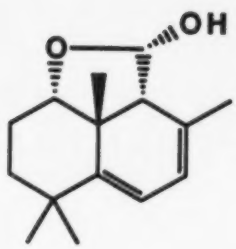
230

Sodium acetate (13 mg. 0.16 mmol) and PCC (7 mg, 0.03 mmol) were added to a solution of **227** (1.07 mg, 0.0045 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature for 3 hr. Thin-layer chromatography indicated that the starting material had disappeared and a major product was formed. The reaction mixture was filtered through a short column of silica gel, elution with ether : Skelly B (1 : 1). The filtrate was concentrated and the residue was subjected to flash chromatography. Elution with acetone - Skelly B (1 : 6) afforded **230** (1.00 mg, 0.0042 mmol, 94%): IR (CH_2Cl_2, cast): 3432 cm^{-1} (br, md, -OH); ^1H NMR (200 MHz, $CDCl_3$): δ 5.68 (m, 2H, olefinic protons), 4.15 (dd, J_1 = 8.5 Hz, J_2 = 7.2 Hz, 1H, OCH_2CH), 3.45 (dd, J_1 = 10.5 Hz, J_2 = 7.2 Hz, 1H, OCH_2CH), 2.68 (dd, J_1 = 8.5 Hz, J_2 = 10.5 Hz, 1H, OCH_2CH), 2.04 (br s, 1H, OH), 2.02 (pseudo td, J_1 = 13.5 Hz, J_2 = 4.4 Hz, 1H, $OCCH_2CH_2$, ax.), 1.83 (ddd, J_1 = 13.5 Hz, J_2 = 3.8 Hz, J_3 = 3.1, 1H, $OCCH_2CH_2$, eq.), 1.82 (d, J = 1.0 Hz, 3H, $CH{=}CCH_3$), 1.5 - 1.3 (m, 2H, $OCCH_2CH_2$), 1.14 (s, 6H, two CH_3s), 1.09 (s, 3H, CH_3); HRMS M^+: 234.1617 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

(1R*,2R*,4S*,12R*)-7,7,11,12-Tetramethyl-3-oxatricyclo[6.3.1.0^{4,12}] dodeca-8,10-dien-2-ol (231A) and (1R*,2S*,4S*,12R*)-7,7,11,12-tetramethyl-3-oxatricyclo[6.3.1.0^{4,12}]dodeca-8,10-dien-2-ol (231B)



231A



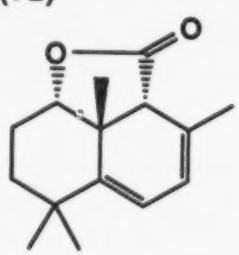
231B

Compound **227** (46 mg, 0.20 mmol) and tris(triphenylphosphine)-ruthenium(II) chloride, $(Ph_3P)_3RuCl_2$, (280 mg, 0.293 mmol) were dissolved in benzene (4 mL). The reaction mixture was stirred at room temperature under argon for 4 days. It was then filtered through a short column of silica gel, elution with ether - Skelly B. The filtrate was concentrated and the residue was subjected to flash chromatography. Elution with acetone - Skelly B (1 : 6) afforded **231B** (27.2 mg, 0.116 mmol, 60%, 66% based on the starting material consumed) and the recovered starting material (4.3 mg, 9%). Compound **231B**: mp 112.0 - 113.0 °C; IR (CH_2Cl_2, cast): 3387 cm^{-1} (br st, hydroxyl); ^1H NMR (360 MHz, $CDCl_3$): δ 5.73 (m, 2H, olefinic protons), 5.09 (dd, J_1 = 6.2 Hz, J_2 = 5.2 Hz, 1H, OC**H**(OH)CH), 4.26 (pseudo t, J = 2.7 Hz, 1H, OC**H**CH_2CH_2), 2.84 (d, J = 5.2 Hz, 1H, D_2O exchangeable, OCH(O**H**)CH), 2.04 (d, J = 6.2 Hz, 1H, OCH(OH)C**H**), 1.93 (dddd, J_1 = 15.1 Hz, J_2 = 13.3 Hz, J_3 = 3.5 Hz, J_4 = 2.7 Hz, 1H, OCHC$\mathbf{H}_2$$CH_2$, ax), 1.88 (d, J = 1.2 Hz, 3H, C=CH-CH=CC$\mathbf{H}_3$), 1.83 (dddd, J_1 = 15.1 Hz, J_2 = 4.8 Hz, J_3 = 3.5 Hz, J_4 = 2.7 Hz, 1H, OCHC$\mathbf{H}_2$$CH_2$, eq), 1.57 (ddd, J_1 = J_2 = 13.2 Hz, J_3 = 4.8 Hz, 1H, OCHCH$_2$C$\mathbf{H}_2$, ax), 1.23 (ddd, J_1 = 13.2 Hz, J_2 = J_3 = 3.5 Hz, 1H, OCHCH$_2$C$\mathbf{H}_2$, eq), 1.11 (s, 3H, angular CH_3), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR BB (75 MHz, acetone-d_6): δ 145.73, 132.73, 119.38, 118.07, 104.52, 84.46, 63.19, 44.97, 35.27, 34.62,

31.16, 28.88, 23.14, 22.82, 22.39; HRMS M+: 234.1620 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

Upon standing in $CDCl_3$, another set of resonance signals appeared in each of the ^1H and ^{13}C NMR spectra which was attributed to **231A**: ^1H NMR (360 MHz, $CDCl_3$): δ 5.92 (dq, J_1 = 5.6 Hz, J_2 =1.5 Hz, 1H, C=CH-C**H**=CCH$_3$), 5.78 (d, J = 5.6 Hz, 1H, C=C**H**-CH=CCH$_3$), 5.25 (dd, J_1 = 12.1 Hz, J_2 = 6.1 Hz, 1H, OC**H**(OH)CH), 3.97 (pseudo t, J = 3.0 Hz, 1H, OC**H**CH$_2$CH$_2$), 2.81 (d, J = 12.1 Hz, 1H, D_2O exchangeable, OCH(O**H**)CH), 2.24 (d, J = 6.1 Hz, 1H, OCH(OH)C**H**), 1.93 (m, 1H, OCHC**H**$_2$CH$_2$, ax), 1.84 (d, J = 1.5 Hz, 3H, C=CH-CH=CC**H**$_3$), 1.80 (m, 1H, OCHC**H**$_2$CH$_2$, eq), 1.55 (ddd, J_1 = J_2 = 13.2 Hz, J_3 = 4.8 Hz, 1H, OCHCH$_2$C**H**$_2$, ax), 1.26 (ddd, J_1 = 13.2 Hz, J_2 = J_3 = 3.5 Hz, 1H, OCHCH$_2$C**H**$_2$, eq), 1.10 (s, 3H, angular CH$_3$), 1.09 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$); ^{13}C NMR BB (75 MHz, $CDCl_3$):δ 104.42, 63.19.

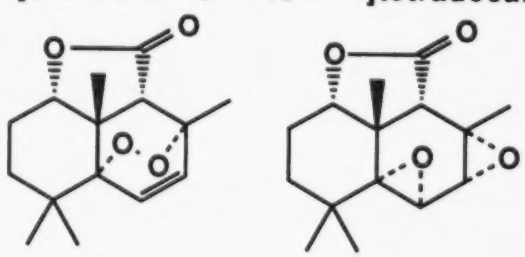
(1R*,4S*,12R*)-7,7,11,12-Tetramethyl-3-oxatricyclo[6.3.1.0^{4,12}]-dodeca-8,10-dien-2-one (72)



Jones reagent was slowly added to a solution of **231** (32.40 mg, 0.138 mmol) in acetone (2 mL) at 0°C until the reaction mixture remained orange in color and stirring was continued for another 5 min. Water (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The extracts were washed sequentially with H_2O, $NaHCO_3$ and saturated sodium chloride

solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with acetone - Skelly B (1 : 6) afforded **72** (12.10 mg, 0.052 mmol, 38%): mp 90.0 - 91.5 °C; IR (CH_2Cl_2, cast): 3070 (w, olefinic C-H), 1771 cm^{-1} (st, C=O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.86 (d, J = 5.8 Hz, 1H, C=C**H**-CH=CCH_3), 5.81 (dq, J_1 = 5.8 Hz, J_2 =1.5 Hz, 1H, C=CH-C**H**=CCH_3), 4.40 (dd, J_1 = 3.1 Hz, J_2 =2.4 Hz, 1H, OC**H**CH_2CH_2), 2.63 (s, 1H, OC(O)C**H**), 2.05 (m, 2H, OCH$C\mathbf{H}_2CH_2$), 1.97 (d, J = 1.5 Hz, 3H, C=CH-CH=$CC\mathbf{H}_3$), 1.52 (ddd, J_1 = J_2 = 13.6 Hz, J_3 = 5.7 Hz, OCH$CH_2C\mathbf{H}_2$), 1.29 (ddd, J_1 = 13.6 Hz, J_2 = J_3 = 3.5 Hz, OCH$CH_2C\mathbf{H}_2$), 1.20 (s, 3H, $C\mathbf{H}_3$), 1.12 (s, 3H, $C\mathbf{H}_3$), 1.09 (s, 3H, $C\mathbf{H}_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 176.49 (p), 141.91 (p), 127.76 (p), 120.89 (ap), 119.92 (ap), 85.12 (ap), 56.46 (ap), 43.24 (p), 34.60 (p), 33.13 (p), 30.50 (ap), 28.06 (ap), 22.68 (ap), 22.29 (ap), 21.60 (p); HRMS M^+: 232.1457 (calcd. for $C_{15}H_{20}O_2$: 232.1463).

(1R*,2S*,5S*,9R*,14S*)-1,8,8,14-Tetramethyl-4,12,13-trioxa-tetracyclo[7.2.2.1^{2,9}.0^{5,14}]tetradec-10-en-3-one (131) and (1S*,4S*,8R*,10S*,11R*,13S*,14S*)-7,7,13,14-tetramethyl-3,9,12-trioxapentacyclo[6.5.1.0^{4,14}.0^{8,10}.0^{11,13}]tetradecan-2-one (232)



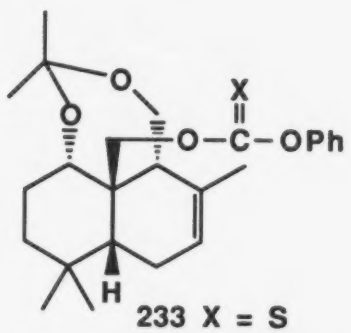
131 **232**

A solution of **72** (2.67 mg, 0.011 mmol) and methylene blue (0.2 mg, 0.0005 mmol) in chloroform (20 mL) was added to the reaction vessel, as shown in Fig. 2-3. Cooling water (below 8 °C) was introduced to the condenser

and the concave of the vessel. Fine bubbles of O_2 gas was generated at the surfaces of the fritted glass when a slight pressure of O_2 was applied. After 20 min of bubbling, two tungsten lamps (200-W each) which were placed on the opposite sides of the vessel were turned on. The reaction was monitored with thin-layer chromatography. After 3 days, the reaction mixture was concentrated and subjected to flash chromatography. Elution with acetone - Skelly B (5 : 95) afforded **131** (0.91 mg, 0.0034 mmol, 30%) and **232** (0.81 mg, 0.0031 mmol, 27%). Applying the same procedure as described above, another run was carried out with 1.26 mg of **72** (0.0056 mmol) and 0.7 mg of methylene blue (0.0027 mmol) in chloroform (20 mL). After 30 hr, compound **131** (1.42 mg, 0.0054 mmol, 95%) was isolated. Compound **131**: IR ($CDCl_3$, cast): 1765 cm^{-1} (st, C=O); ^1H NMR (360 MHz, $CDCl_3$): 6.68 (d, J = 8.6 Hz, 1H, olefinic proton), 6.45 (d, J = 8.6 Hz, 1H, olefinic proton), 4.37 (pseudo t, J = 6.3 Hz, 1H, OC**H**), 2.18 (dddd, J_1 = 14.6 Hz, J_2 = 9.0 Hz, J_3 = 6.3 Hz, J_4 = 4.1 Hz, 1H, OCHC**H**$_2$CH$_2$), 2.15 (s, 1H, OC(O)C**H**), 2.08 (dddd, J_1 = 14.6 Hz, J_2 = 8.7 Hz, J_3 = 6.3 Hz, J_4 = 4.2 Hz, 1H, OCHC**H**$_2$CH$_2$), 1.75 (ddd, J_1 = 14.2 Hz, J_2 = 8.7 Hz, J_3 = 4.1 Hz, 1H, OCHCH$_2$C**H**$_2$), 1.70 (s, 3H, C**H**$_3$), 1.30 (ddd, J_1 = 14.2 Hz, J_2 = 9.0 Hz, J_3 = 4.2 Hz, 1H, OCHCH$_2$C**H**$_2$), 1.22 (s, 3H, C**H**$_3$), 1.20 (s, 3H, C**H**$_3$), 1.03 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 174.26 (p), 137.02 (ap), 132.17 (ap), 83.42 (p), 82.05 (ap), 74.47 (p), 54.36 (ap), 46.79 (p), 34.70 (p), 30.72 (p), 28.03 (ap), 26.69 (ap), 26.21 (ap), 23.12 (p), 18.66 (ap); HRMS M^+: 264.1361 (calcd. for $C_{15}H_{20}O_4$: 264.1362). Compound **232**: IR ($CDCl_3$, cast): 1781 cm^{-1} (st, C=O); ^1H NMR (360 MHz, $CDCl_3$): 4.22 (pseudo t, J = 4.2 Hz, OC**H**), 3.41 (d, J = 2.4 Hz, 1H, epoxide proton), 3.15 (d, J = 2.4 Hz, 1H, epoxide proton), 2.34 (s, 1H, OC(O)C**H**), 2.03 (m, 2H, OCHC**H**$_2$CH$_2$), 1.78 (ddd, J_1 = 14.0 Hz, J_2 = J_3 = 7.0 Hz, 1H, OCHCH$_2$C**H**$_2$), 1.47 (s, 3H, C**H**$_3$), 1.40 (s, 3H, C**H**$_3$), 1.29 (ddd, J_1 = 14.0 Hz, J_2 = J_3 = 4.9 Hz, 1H, OCHCH$_2$C**H**$_2$), 1.15 (s, 3H, C**H**$_3$), 0.77 (s, 3H,

CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 171.69 (p), 82.09 (ap), 66.09 (p), 53.66 (ap), 53.00 (ap), 49.95 (ap), 48.78 (p), 43.98 (p), 33.86 (p), 31.94 (p), 25.45 (ap), 25.10 (ap), 24.93 (ap), 22.47 (p), 21.23 (ap); HRMS M^+: 264.1358 (calcd. for $C_{15}H_{20}O_4$: 264.1362).

(1R*,5R*,9S*,14R*)-2,6,6,11,11-Pentamethyl-14-(phenoxythiocarbonyloxymethyl)-10,12-dioxatricyclo[7.4.1.0^{5,14}]-tetradec-2-ene (233) and (1R*,5R*,9S*,14R*)-2,6,6,11,11-pentamethyl-14-(phenoxycarbonyloxymethyl)-10,12-dioxatricyclo[7.4.1.0^{5,14}]-tetradec-2-ene (234)

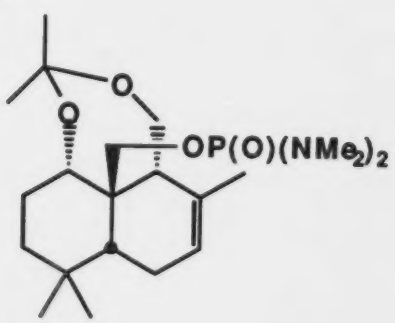


233 X = S
234 X = O

Pyridine (60 μL, 0.73 mmol) and phenyl chlorothionoformate (85 μl, 0.61 mmol) were added to a solution of **213** (32 mg, 0.11 mmol) in THF (1 mL) at 0 °C and the resulting reaction mixture was stirred at room temperature for 3 hr. Saturated $NaHCO_3$ solution (3 mL) was added and the resulting mixture was extracted with ether. The extracts were washed with water and saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography on silica gel with ether and Skelly B (1 : 10) afforded **233** (20 mg, 0.0465 mmol, 43%), **234** (3.54 mg, 0.0086 mmol, 8%) and the recovered starting material (6.5 mg, 20%). Compound **233**: IR (MeOH, cast): 1218 and

1198 cm^1 (st, C-O bonds and C=S bond); ^1H NMR (360 MHz, acetone-d_6): δ 7.47 (m, 2H, phenyl), 7.32 (m, 1H, phenyl), 7.18 (m, 2H, phenyl), 5.75 (m, 1H, $CH{=}CCH_3$), 4.26 (d, J = 11.3 Hz, 1H, $CCH_2OC(S)OPh$), 4.19 (d, J = 11.3 Hz, 1H, $CCH_2OC(S)OPh$), 4.18 (m, 1H, $OCHCH_2CH_2$), 3.74 (dd, J_1 = 12.7 Hz, J_2 = 9.8 Hz, 1H, OCH_2CH), 3.43 (dd, J_1 = 12.7 Hz, J_2 = 3.8 Hz, 1H, OCH_2CH), 2.39 (dd, J_1 = 9.8 Hz, J_2 = 3.8 Hz, 1H, OCH_2CH), 1.72 (s, 3H, $CH{=}CCH_3$), 1.26 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); HRMS: 354.1663 (M^+ - $C_4H_8O_2$, calcd. for $C_{21}H_{26}O_2S$: 342.1653). Compound **234**: IR (MeOH, cast): 1762 cm^{-1} (st, C=O), 1247 (st, C-O of the carbonate), 1234 (st, C-O of the carbonate), 1211 cm^{-1} (st, C-O of the acetal); ^1H (360 MHz, acetone-d_6): δ 7.43 (m, 2H, phenyl), 7.29 (m, 1H, phenyl), 7.21 (m, 2H, phenyl), 5.75 (m, 1H, $CH{=}CCH_3$), 4.20 (m, 1H, $OCHCH_2CH_2$), 4.00 (d, J = 11.0 Hz, 1H, $CCH_2OC(O)OPh$), 3.86 (d, J = 11.0 Hz, 1H, $CCH_2OC(O)OPh$), 3.64 (dd, J_1 = 12.8 Hz, J_2 = 10.1 Hz, 1H, OCH_2CH), 3.42 (dd, J_1 = 12.8 Hz, J_2 = 3.9 Hz, 1H, OCH_2CH), 2.42 (dd, J_1 = 10.1 Hz, J_2 = 3.9 Hz, 1H, OCH_2CH), 1.73 (s, 3H, $CH{=}CCH_3$), 1.29 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); HRMS: 384.2299 (M^+ - CH_2O, calcd. for $C_{24}H_{32}O_4$: 384.2301).

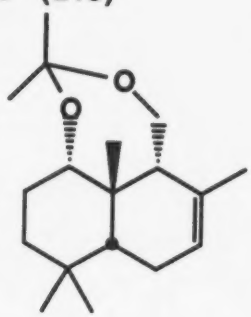
(1R*,5R*,9S*,14S*)-2,6,6,11,11-Pentamethyl-14-tetramethyl-diamidophosphoroxymethyl-10,12-dioxatricyclo[7.4.1.$0^{5,14}$]-tetradec-2-ene (236)



n-Butyllithium (1.6 M in hexanes, 0.18 mL, 0.28 mmol) was added to a solution of compound **213** (57.85 mg, 0.196 mmol) in DME - TMEDA (4 : 1, 1 mL) at 0 °C under argon. After 15 min at room temperature, *N,N*-dimethylphosphoramidic dichloride (0.12 mL, 1.0 mmol) was added and the reaction mixture was stirred at room temperature under argon for 10 hr. Dimethylamine (1 mL) was added at 0 °C and stirring was continued at this temperature for another 20 min. The reaction mixture was poured into ice water and extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with Et_3N. Elution with acetone and Skelly B (1 : 5) afforded **236** (73.7 mg, 0.196 mmol, 100%): IR (acetone-d_6, cast): 1220 (st, P=O), 1075 cm^{-1} (st, C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.73 (m, 1H, C**H**=C), 4.27 (d, J = 6.8 Hz, 1H, OC**H**), 3.70 (dd, J_1 = 12.3 Hz, J_2 = 10.5 Hz, 1H, OC$\mathbf{H}_2$CH), 3.61 (dd, J_1 = 10.2 Hz, J_2 = 5.0 Hz, 1H, POC$\mathbf{H}_2$), 3.33 (dd, J_1 = 12.3 Hz, J_2 = 4.0 Hz, 1H, OC$\mathbf{H}_2$CH), 3.30 (dd, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H, POC$\mathbf{H}_2$), 2.63 (d, J = 9.8 Hz, 6H, PNC$\mathbf{H}_3$), 2.61 (d, J = 9.9 Hz, 6H, PNC$\mathbf{H}_3$), 2.59 (dd, J_1 = 10.5 Hz, J_2 = 4.0 Hz, 1H, OCH$_2$C**H**), 2.12 (dddd, J_1 = 15.1 Hz, J_2 = 9.2 Hz, J_3 = 6.8 Hz, J_4 = 3.1 Hz, 1H, OCHC$\mathbf{H}_2$CH$_2$, ax), 1.98 (m, 2H, CHC$\mathbf{H}_2$CH=C), 1.74 (d, J = 0.86 Hz, 3H, CH=CC$\mathbf{H}_3$), 1.69 (dddd, J_1 = 15.1 Hz, J_2 = J_3 = 9.0 Hz, J_4 = 1.2 Hz, 1H, OCHC$\mathbf{H}_2$CH$_2$, eq), 1.53 (ddd, J_1 = 14.1 Hz, J_2 = 9.0 Hz, J_3 = 3.1 Hz, 1H, OCHCH$_2$C$\mathbf{H}_2$, eq), 1.41 (ddd, J_1 = 14.1 Hz, J_2 = J_3 = 9.0 Hz, OCHCH$_2$C$\mathbf{H}_2$, ax), 1.28 (s, 3H, C$\mathbf{H}_3$), 1.24 (s, 3H, C$\mathbf{H}_3$), 1.16 (s, 3H, C$\mathbf{H}_3$), 0.96 (s, 3H, C$\mathbf{H}_3$), 0.80 (dd, J_1 = 9.5 Hz, J_2 = 7.5 Hz, 1H, C**H**CH$_2$CH=C); ^{13}C NMR APT (75 MHz, acetone-d_6): δ 136.09 (p), 125.89 (ap), 101.00 (p), 71.15 (d, J = 5.1 Hz, p), 68.15 (ap), 62.01 (p), 49.95 (ap), 48.27 (ap), 44.83 (p), 36.83 (d, J = 3.5 Hz, ap), 36.73 (d, J = 3.5 Hz, ap), 34.65 (ap), 34.57 (p), 32.46 (p), 26.63 (p), 25.77 (ap), 25.59

(p), 25.02 (ap), 23.91 (ap), 22.98 (ap); HRMS M^+: 428.2800 (calcd. for $C_{22}H_{41}O_4N_2P$: 428.2804).

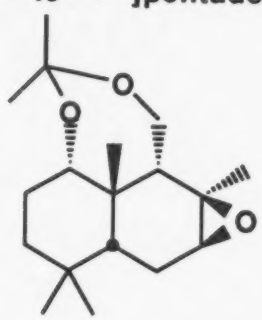
(1R*,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxatricyclo-[7.4.1.0^{5,14}]tetradec-2-ene (215)



Compound **236** (0.158 g, 0.40 mmol) in THF (0.5 mL) was slowly added to a blue solution of lithium (about 15 mg, 2.1 mmol) in ethylamine (5 mL) at 0 °C under argon. After 10 min, water was added and the resulting mixture was extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution (2 x 10 mL), dried, filtered and concentrated. Flash column chromatography with Skelly B afforded **215** (94.5 mg, 0.34 mmol, 85%) as an colorless oil. Further elution with ethyl acetate - Skelly B (15 : 85) afforded **213** (4.7 mg, 0.016 mmol, 4%). Compound **215**: IR (acetone-d_6, cast): 1220 cm^{-1} (st, C-O); ^1H NMR (300 MHz, acetone-d_6): δ 5.68 (m, 1H, C**H**=CCH_3), 3.93 (d, J = 6.2 Hz, 1H, OC**H**CH_2CH_2), 3.70 (dd, J_1 = 12.7 Hz, J_2 = 9.3 Hz, 1H, OCH_2CH), 3.44 (dd, J_1 = 12.7 Hz, J_2 = 3.5 Hz, 1H, OCH_2CH), 2.0 (m, 3H, OCHCH_2CH_2, OCH_2C**H**, C**H**$_2$CH=C), 1.70 (pseudo t, J = 2.0 Hz, 3H, CH=CCH_3), 1.62 (dddd, J_1 = 14.5 Hz, J_2 = J_3 = 7.4 Hz, J_4 = 1.8 Hz, 1H, OCHC**H**$_2$$CH_2$, eq), 1.52 (ddd, J_1 = 13.0 Hz, J_2 = 7.5 Hz, J_3 = 5.5 Hz, 1H, OCHCH_2C**H**$_2$, eq), 1.35 (ddd, J_1 = 13.0 Hz, J_2 = J_3 = 7.4 Hz, 1H, OCHCH_2C**H**$_2$,

ax), 1.28 (s, 3H, CH_3), 1.20 (d, J = 0.7 Hz, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, acetone-d_6): δ 135.60 (p), 125.66 (ap), 100.74 (p), 73.07 (ap), 62.05 (p), 57.43 (ap), 51.37 (ap), 41.13 (p), 33.95 (ap), 33.87 (ap), 33.16 (p), 27.10 (p), 27.06 (ap), 26.91 (ap), 26.36 (p), 23.15 (ap), 23.06 (ap); HRMS: 278.2240 (M^+, calcd. for $C_{18}H_{30}O_2$: 278.2246), 248.2131 ($M^+ - CH_2O$, calcd. for $C_{17}H_{28}O$: 248.2140).

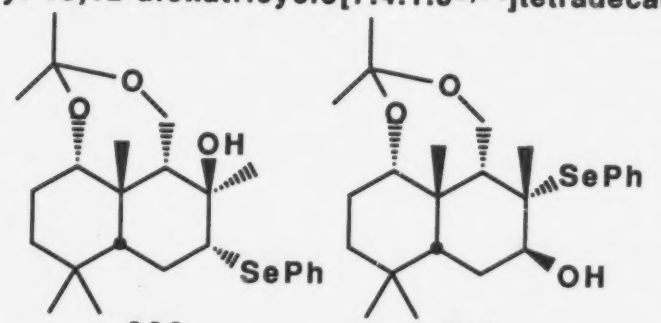
(1S*,6S*,10R*,12S*,14R*,15S*)-4,4,9,9,14,15-Hexamethyl-3,5,13-trioxatetracyclo[8.4.1.0^{6,15}.0^{12,14}]pentadecane (237)



Compound **215** (8.11 mg, 0.029 mmol) was dissolved in CH_2Cl_2 (1 mL). To this solution were added saturated $NaHCO_3$ solution (0.5 mL) and MCPBA (80-85%, 13 mg, 0.6 mmol). The resulting heterogeneous reaction mixture was stirred at room temperature for 1 hr. Excess MCPBA was destroyed with sodium sulfite and the reaction mixture was extracted with ether. The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash column chromatography on silica gel pre-treated with triethylamine, elution with ether : Skelly B (1 : 10) afforded **237** (7.65 mg, 0.026 mmol, 89%): IR ($CHCl_3$, cast): 1221 (st, C-O), 1083 cm^{-1} (st, C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 3.78 (m, 3H, OC**H** and OCH_2), 3.06 (d, J = 3.8 Hz, 1H, epoxide OC**H**), 2.00 (m, 3H), 1.82 (dd, J_1 = 8.2 Hz, J_2 = 3.3 Hz, OCH_2CH),

1.6 - 1.4 (m, 4H), 1.40 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 100.04 (p), 72.52 (ap), 62.20 (p), 60.07 (ap), 58.10 (p), 53.81 (ap), 43.27 (ap), 40.32 (p), 33.37 (ap), 32.57 (ap), 32.23 (p), 31.89 (p), 27.09 (ap, two carbon signals at 27.24 and 27.12 in a 1 : 1 mixture of $CDCl_3$ - C_6D_6), 26.38 (p), 25.55 (p), 22.66 (ap), 22.37 (ap); HRMS: 264.2078 (M^+ - CH_2O, calcd. for $C_{17}H_{28}O_2$: 264.2089); CIMS: 265.3 (M^+ - CH_2O + 1).

(1R*,2R*,3R*,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-3-phenylselenyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]tetradecan-2-ol (238) and (1R*,2S*,3S*,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-2-phenylselenyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]tetradecan-3-ol (240)



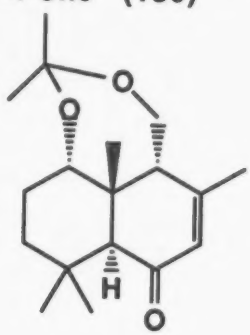
238 240

Sodium borohydride (47 mg, 1.2 mmol) was added in batches to a suspension of diphenyl diselenide (270 mg, 0.87 mmol) in EtOH (4 mL) at 0 °C until the yellow color of diphenyl diselenide disappeared. The resulting solution was stirred at room temperature for 20 min so that any remaining $NaBH_4$ would be consumed by the solvent. A solution of **237** (161 mg, 0.55 mmol) in EtOH (4 mL) was added and the reaction mixture was refluxed under argon for 60 hr. After cooling with an ice-bath, saturated aqueous NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with ether (3 x 20

mL). The extracts were washed with saturated NaCl solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with Et_3N. Gradient elution with ether - Skelly B (1 : 10 to 1 : 3) afforded **240** (14 mg, 6%) and **238** (194 mg, 79%). Compound **238**: IR (CH_2Cl_2, cast): 3445 (br, md, -OH), 3060 (w, aromatic C-H), 1265 (st, C-O), 1221 (st, C-O), 1121 cm^{-1} (st, C-O); ^1H NMR (400 MHz, C_6D_6): δ 7.54 (m, 2H, Phenyl), 6.97 (m, 3H, phenyl), 4.30 (pseudo, t, J = 12.6 Hz, 1H, OCH_2CH), 3.94 (m, 1H, $OCHCH_2CH_2$), 3.80 (dd, J_1 = 12.6 Hz, J_2 = 5.7 Hz, 1H, $OCHCH_2CH_2$), 3.49 (dd, J_1 = 11.9 Hz, J_2 = 7.7 Hz, 1H, CHSePh), 2.38 (m, 2H, $CHCH_2CHSePh$), 1.87 (m, 4H), 1.58 (m, 1H), 1.42 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.13 (m, 1H), 1.06 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, acetone-d_6): δ 134.09 (ap), 132.42 (p), 129.87 (ap), 127.76 (ap), 100.88 (p), 75.65 (p), 72.77 (ap), 64.33 (p), 61.78 (ap), 53.58 (ap), 47.31 (ap), 42.11 (p), 34.80 (ap), 34.26 (p), 33.23 (ap), 32.89 (p), 31.70 (p), 31.63 (ap), 30.96 ap), 26.24 (p), 24.98 (ap), 23.63 (ap); HRMS: 452.1861 (M^+, calcd. for $C_{24}H_{36}O_3{}^{80}Se$: 452.1830), 450.1875 (M^+, calcd. for $C_{24}H_{36}O_3{}^{78}Se$: 450.1838). Compound **240**: IR (KBr): 3320 (br, st, -OH), 3070 (md, C-H, phenyl), 1580 cm^{-1} (m, aromatic ring skeleton); ^1H NMR (300 MHz, acetone-d_6): δ 7.61 (m, 2H, phenyl), 7.32 (m, 3H, phenyl), 5.66 (br s, 1H, -OH), 4.17 (dd, J_1 = 13.8 Hz, J_2 = 3.8 Hz, 1H, OCH_2CH), 4.09 (dd, J_1 = 13.8 Hz, J_2 = 7.5 Hz, 1H, OCH_2CH), 3.91 (dd, J_1 = 9.8 Hz, J_2 = 6.4 Hz, 1H, $OCHCH_2CH_2$), 3.55 (pseudo t, J = 3.7 Hz, 1H, $HOCHCH_2CH$), 2.16 (psudeo dt, $J_1 = J_2$ = 13.8 Hz, J_3 = 3.7 Hz, 1H, $HOCHCH_2CH$), 1.99 (dd, J_1 = 7.5 Hz, J_2 = 3.8 Hz, 1H, OCH_2CH), 1.82 (dd, J_1 = 13.8 Hz, J_2 = 3.6 Hz, 1H, $HOCHCH_2CH$), 1.70 (pseudo td, J_1 = 13.8 Hz, $J_2 = J_3$ = 3.6 Hz, 1H, $HOCHCH_2CH$), 1.69 - 1.51 (m, 3H, OCH_2CH_2), 1.45 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.40 - 1.35 (m, 1H, $OCHCH_2CH_2$), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.74 (s,

3H, CH_3); ^{13}C APT (75 MHz, acetone-d_6): δ 135.44 (ap), 131.31 (p), 129.96 (ap), 128.22 (ap), 103.02 (p), 76.49 (ap), 73.39 (p), 60.75 (p), 58.12 (ap), 54.45 (ap), 46.44 (ap), 45.32 (p), 34.74 (p), 34.48 (ap), 34.02 (ap), 33.21 (p), 30.92 (ap), 30.78 (p), 27.59 (p), 24.95 (ap), 24.06 (ap); HRMS: 452.1820 (M^+, calcd. for $C_{24}H_{36}O_3{}^{80}Se$: 452.1830), 450.1822 (M^+, calcd. for $.C_{24}H_{36}O_3{}^{78}Se$: 450.1838).

(1R*,5S*,9S*,14R*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxatricyclo-[7.4.1.0^{5,14}]tetradec-2-en-4-one (156)



Chromium trioxide (191 mg, 1.9 mmol) was added to pyridine (1 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirring was continued under argon for another 10 min. A solution of **237** (51.20 mg, 0.113 mmol) in pyridine (2 mL) was added. The resulting reaction mixture was stirred at room temperature under argon for 20 hr, then filtered through a thin pad of florisil (60 - 100 mesh), washed with ether. The filtrate was concentrated with a rotary evaporator equipped with a dry-ice condenser. The residue was dissolved in methanol (3 mL). To this methanolic solution was added sodium hydroxide solution (1N, 0.4 mL). The reaction mixture was stirred at room temperature for 4 hr, then extracted with ether (3x20 mL). The extracts were washed saturated sodium chloride solution, dried, filtered and

concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with triethylamine. Elution with ethyl acetate - Skelly B (5 : 95) afforded diene **219** (2.2 mg, 7%) and the desired enone **156** (16.10 mg, 49%): IR (KBr): 1668 cm^{-1} (St, C=O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.71 (d, J = 1.3 Hz, 1H, olefinic), 3.93 (dd, J_1 = 12.6 Hz, J_2 = 10.1 Hz, 1H, OCH_2CH), 3.73 (d, J = 4.7 Hz, 1H, $OCHCH_2CH_2$), 3.45 (dd, J_1 = 12.6 Hz, J_2 = 2.9 Hz, 1H, OCH_2CH), 2.71 (s, 1H, CHC=O), 2.03 (dd, J_1 = 10.1 Hz, J_2 = 2.9 Hz, 1H, OCH_2CH), 1.90 (d, J = 1.3 Hz, 3H, $CH=CCH_3$), 1.87 (m, 2H), 1.42 (m, 2H), 1.37 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 199.96 (p), 154.38 (p), 128.50 (ap), 100.71 (p), 73.15 (ap), 59.32 (p), 58.68 (ap), 50.90 (ap), 43.80 (p), 36.36 (p), 34.43 (ap), 31.85 (p), 25.79 (ap), 24.74 (p), 23.91 (ap), 23.16 (ap), 22.99 (ap), 22.77 (ap); HRMS: 292.2036 (M^+, calcd. for $C_{18}H_{28}O_3$: 292.2039), 262.1967 ($M^+ - CH_2O$, calcd. for $C_{17}H_{26}O_2$: 262.1933).

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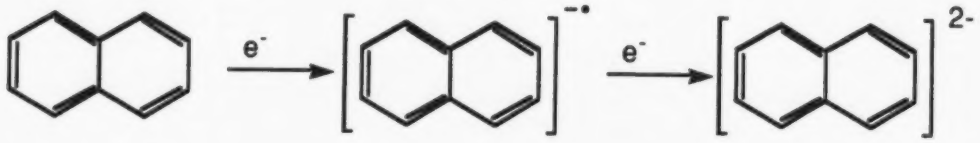
Chapter Three

Reduction of *N,N,N',N'*-Tetramethylphosphorodiamidates with Lithium Naphthalenide

Introduction

The radical anions of aromatic hydrocarbons of alkali metals[1-3] have found wide applications in organic synthesis, organometallic, inorganic, environmental[4] and analytical chemistry.[5] The most commonly used metals are sodium and lithium, although other metals, like potassium and cesium, have also been tested. The aromatic hydrocarbon used include biphenyl, naphthalene, anthracene, perylene, phenanthrene, pyrene and tetracene, and their derivatives. As reducing agents, the radical anions of biphenyl and naphthalene in THF are almost as powerful as the corresponding metals themselves. This makes them the first choices among those arenes tested. 4,4'-Di-*tert*-butylbiphenyl is preferred over its parent compound for its solidity and ease of handling, while α-(*N,N*-dimethylamino)naphthalene is used in place of naphthalene to facilitate the separation of the products when they are as nonpolar as naphthalene.[6] For the sake of simplicity, only lithium naphthalenide (LN) will be used in the following discussion unless otherwise indicated.

Scheme 3-1



When the metal is dissolved in a solution of naphthalene, with THF being the most commonly used ethereal solvent, a deep green to blue solution of the radical anion is formed, like other "electron solutions". If more than one equivalent of the metal is added, the dianion will be produced (Scheme 3-1),

although its presence can never be completely excluded even with less than one equivalent of lithium, due to the disproportionation of the radical anion. Only in highly polar solvents, like HMPA, will the radical anions exist free. In THF and other ethereal solvents, they exist mainly as ion pairs with the countercations. The dissociation of these ion pairs is favored with smaller cations, *e.g.* Li^+, due to higher heat of solvation. The concentration of the radical anions can be estimated by electric potential titration.[7,8]

The chemical reactions of these radical anions can be classified into two general classes, namely, proton abstraction reactions, due to the high basicity of the radical anion, and single electron transfer (SET) reactions. As a strong base, it was estimated that these radical anions were effective in abstracting protons from compounds having a pK_a less than 33. Cases of proton abstraction from aldehydes, ketones, carboxylic acids, esters, carboxylates, nitriles and epoxides are known in the literature, although the reactions might be complicated by the SET mechanism. The majority of the radical anion reactions involved the SET reactions. For this purpose and in certain cases, a catalytic amount instead of a stoichiometric equivalent of the aromatic hydrocarbon can be used in conjunction with the metal powder to effect the SET reactions.[9-11]

The C-C σ-bonds in alkanes are, as expected, inert to radical anions. Only those which after reduction will give very stable radicals or anions can be reduced. 1,2-Di-(α-naphthyl)-ethane was reduced by sodium biphenyl to give α-methylnaphthalene after work-up.

The most common reactions with simple alkenes and polyenes are polymerization reactions. This was successfully applied to the preparation of some important classes of polymers. The reaction mechanism could either be free radical or anionic.[12] Besides polymerization, the alkene can also add to a

carbanion to form an addition product. When another reducible functional group is present in the same molecule, an intramolecular free radical addition to the C=C double bond may occur to form a new ring.

Terminal alkynes will be deprotonated by the radical anions. Having no acidic hydrogen, internal alkynes accept either one or two electron(s) to become radical anions[13] or dianions, respectively. Allenes react in the same manner.[14]

The most commonly seen examples of lithium naphthalenide SET reactions are probably the reductions of alkyl, silyl,[15] vinyl[16] or aryl[17,18] halides, dihalides[19-21] and pseudo halides (ArX, RX or R_3SiX, X = F, Cl, Br, I, CN[22,23], SePh). These reductions could proceed *via* different pathways to give a variety of products. The $R^{\cdot}$[24] or R^- formed can abstract a hydrogen atom or a proton from the media to yield the reduced product R-H, add to another functional group in the same molecule[24], couple with the naphthalenide radical anion to form alkylated naphthalenes or alkylated dihydronaphthalenes or dimerize to give R-R. If a leaving group is present at the β-position, α,β–elimination will occur to give a C=C double bond[25]. When the leaving group is positioned at the δ-position, fragmentation of the chain or ring will happen to produce two C=C double bonds.[6,26] These reductions are usually very fast and proceed at low temperatures, thus allowing the trapping of the anions produced with a variety of electrophiles. Some synthons based on the alkyl halides and dihalides were delicately designed and incorporated into synthetic schemes.[10,19,21]

Reduction of epoxides is very straightforward, producing dianions from the C-O bond cleavage, which can be trapped with other electrophiles, or give alcohols upon quenching with a proton source.[27] Carbon-nitrogen bonds in aziridines and azetidines can also be reduced to give *N*-lithio-2-lithio- and *N*-

lithio-3-lithio- alkylamines, respectively.[28,29] Ordinary ethers, like DME, THF, do not react with lithium naphthalenide. This is why the reagent can be stored in these solvents and kept at around 0 °C for weeks. At elevated temperatures, ethers are reduced to give alcohols.[30] Simple acetals are also unreactive towards the radical anions. But allylic acetals can be reduced to give masked homoenolates.[31]

Table 3-1. Reactions of sodium naphthalenide with aromatic carbonyl compounds.

Compound	1,2-Diol (%)[a]	Monool (%)[a]
benzaldehyde	1,2-diphenyl-1,2-ethanediol (88)	benzyl alcohol (7)
p-tolualdehyde	1,2-di(*p*-tolyl)-1,2-ethanediol (90)	*p*-methylbenzyl alcohol (1)
p-anisaldehyde	1,2-di*p*-methoxyphenyl)-1,2-ethanediol (90)	*p*-methoxybenzyl alcohol (1)
p-chlorobenzaldehyde[b]	----	----
cinnamaldehyde[b]	----	----
benzophenone	tetraphenyl-1,2-ethanediol (7)	benzhydrol (90)
p-benzoquinone	----	hydroquinone (92)

[a] Yields are based on carbonyl compound.
[b] Polymeric products formed.

Aromatic aldehydes and aromatic ketones without an α-hydrogen react with lithium naphthalenide to give primarily the corresponding monools and reductive coupling products as diols[32] (Table 3-1). With aliphatic aldehydes and ketones, the competitive deprotonation may give the enolates. Upon quenching with a proton source, the carbonyl compounds would be recovered.

In their studies of a few selective ketones and aldehydes, Holy and co-workers found that the deprotonation accounted for 18-59 % of the starting carbonyl compounds (Table 3-2). The major difference from the aromatic aldehydes and ketones is the tendency to form alkylated and dialkylated 1,4-dihydronaphthalenes[33] (Scheme 3-2).

Table 3-2. Reactions of aliphatic carbonyl compounds with sodium naphthalenide

Carbonyl Compound	Reductive Coupling[a](%)	Monohydroxy-alkylation[a] (%)	Dihydroxy-alkylation[a](%)	Recovered SM (%)
3-pentanone	----	1-(pentan-3-ol)-1,4-dihydronaphthalene (6)	1,4-bis(pentan-3-ol)-1,4-dihydro-naphthalene (35)	59
pentanal	5,6-decane-diol (7)	1-(pentan-1-ol)-1,4-dihydronaphthalene (6)	1,4-bis(pentan-1-ol)-1,4-dihydro-naphthalene (35)	52
2,2-dimethyl-propanal	----	1-(2,2-dimethyl-propan-1-ol)-1,4-dihydronaphthalene (18)	1,4-bis(2,2-dimethyl propan-1-ol)-1,4-di-hydronaphthalene (65)	18

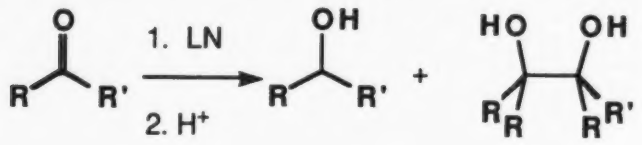
[a]Yields are based on carbonyl compounds.

Carboxylic acids with α-hydrogen and their carboxylates react with lithium naphthalenide to give enolate dianions[34] which can be trapped with electrophiles. If possessing an α-hydrogen, their esters also undergo deprotonation reactions. Thus, the major portion of these esters could be regenerated upon quenching the reactions with water. But this is not the only reaction that occurs. Aliphatic esters also give acylation products of

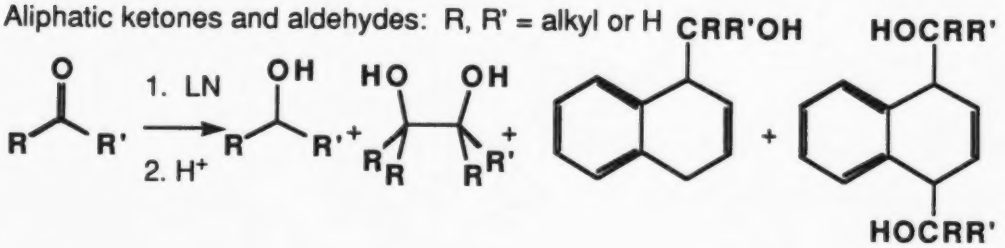
naphthalene, ranging in yield from 11% to 53%. Ethyl benzoate gave benzil and benzoin as the only products derived from the ester.[35]

Scheme 3-2

Aromatic ketones and aldehydes: R, R' = aryl or H



Aliphatic ketones and aldehydes: R, R' = alkyl or H



Sulfur derived functional groups, such as sulfides,[36] sulfoxides,[37] sulfones,[9,37,11] sulfonamides, sulfates,[38] sulfonates,[39] 1,1-bissulfones,[40] 1,1-disulfides,[41] *etc.*, are also widely used in the radical anion reductions and for the generation of carbanions. Numerous tandem synthetic schemes were successfully designed and carried out based on these carbanion strategies, such as Peterson olefination reactions.[42]

The Sn-C bonds in $Bu_3Sn\text{-}CR_3$[43] can be cleaved by lithium naphthalenide to give the alkyl radical first, which can either react as a typical radical, as in the addition to a carbon-carbon double bond, or be further reduced to the carbanion, which upon treatment with a proton source, gives the reduced product. P-X (X = Cl, OR) bonds, as in chlorophosphoranes and phosphinates,[44] can be reduced to put the negative charge on the phosphorus

atom, which can also be trapped with electrophiles. Phosphates react in a similar manner as the sulfates to give carbanions.[45] Even Ar-P bonds can be reduced under more vigorous conditions.[46]

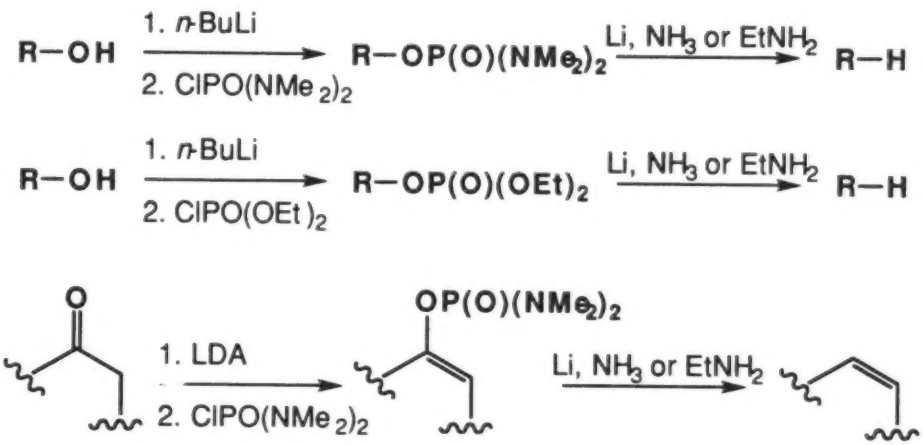
Metal salts, such as halides (MX_n, M = Zn,[47] Ca,[48] Ba,[49] Cu,[50] Ni[51] and Nd[52]), can be reduced to the active, zero-valence state M^0. These active forms of the metals behave quite differently from the corresponding "inactive" ones. Oxidative insertion of the active metal into RX and ArCOX will give RMX and ArCOMX, respectively,[47] which then can react with another mole of RX or ArCOX to give the homocoupled products, or with other electrophiles. Highly reduced organometallics can also be prepared with these reducing agents.[53,54]

Deoxygenation of alcohols ROH into their corresponding alkanes is a frequently required transformation in organic chemistry. Several methods are available to effect this reduction. Ireland and co-workers reported[55] that diethyl phosphates (DEP) and *N,N,N',N'*-tetramethylphosphorodiamidates (TMPDA), derived from alcohols by two-step and one-pot procedures, could be easily reduced by lithium in liquid ammonia or ethylamine (Scheme 3-3). Ketones and aldehydes, when first converted to their corresponding enolates, could be phosphorylated and reduced in the same fashion to afford alkenes (Scheme 3-3). If a transformation from a carbonyl compound to the alkane was desired, a three step procedure could be applied, which required a reduction of the carbonyl compound to the alcohol, followed by phosphorylation and reduction. This offered certain advantages over the Wolff-Kishner method in some cases. They found that, while either derivative was satisfactory for the reductive formation of olefins from the enol esters, the TMPDA grouping was more necessary for the deoxygenation of primary and secondary alcohols. More by virtue of its greater ease of formation than a significant difference in the reduction stage, the DEP grouping appeared better for the reductive removal of

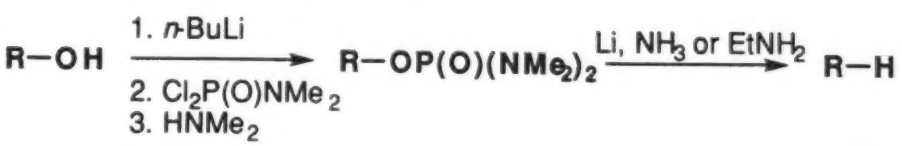
tertiary alcohols. This shortcoming caused by the steric crowding on the alcohol part was later overcome by an efficient modification made in our group.[56] Instead of reacting the alkoxides with *N,N,N',N'*-tetramethyldiamidophosphorochloridate directly, a three-step, one-pot procedure was devised, involving phosphorylation of the alkoxides with a sterically less demanding reagent, *N,N*-dimethylphosphoramidic dichloride (DMPADC), followed by addition of an excess of dimethylamine (Scheme 3-3). This way, some TMPDA derivatives were prepared from sterically congested alcohols, which failed to react with *N,N,N',N'*-tetramethylphosphorodiamidic chloride completely under Ireland's conditions.

Scheme 3-3

Ireland's methods of preparing TMPDAs and DEPs and their reduction



Liu's modification using DMPADC



3β-Cholestanyl TMPDA was used by Ireland to test the stability of this class of compounds. It was found that less than 5% reaction was observed when this compound was treated with CH_3Li - Et_2O (2.5 hr at 25 °C), $LiAlH_4$ - Et_2O (2.5 hr at 25 °C), 1 N KOH - EtOH (15 hr at reflux), and 0.2 N aq. HCl-acetone (2 hr at 25 °C). Prolonged treatment with 0.2 N HCl - acetone (12 hr at 25 °C) resulted in recovery of only 59% of the original TMPDA, but no starting alcohol was found. The regeneration of 3β-cholestanol from its TMPDA was accomplished in quantitative yield after treatment with 5 eq. of *n*-BuLi in *N,N,N',N'*-tetramethylethylenediamine for 30 min at 25 °C. It was obvious that this functional group was stable and hardly underwent any elimination, substitution or hydride reduction reactions. Exceptions were also found. Propargylic TMPDAs undergo substitution reactions with alkylsulfides to yield 2-alkynyl sulfides.[57] Allylic TMPDAs can be deprotonated at the allylic postion and undergo further rearrangement.[58]

Considering the difficulties associated with handling and purifying the very volatile and sometimes dirty ammonia, the volatile and expensive anhydrous $EtNH_2$, especially on a small scale, we decided to look for a more convenient, less costly way to reduce the TMPDAs. Lithium naphthalenide solution in THF seemed to be a natural choice to us, since it could be prepared and stored as a stock solution. The reduction could be done with a simple transfer of aliquots of the reagent to the substrate with a syringe and subsequent stirring at room temperature under argon for a short period of time. We also wanted to see if it would be possible to trap the carbanions produced this way. At the same time, the compatibility of this reagent with a selected number of functional groups would be examined.

Results and Discussion

The solution of lithium naphthalenide in THF was prepared and stored in the refrigerator for later use. The TMPDAs of several classes of compounds were prepared according to Ireland's procedure or our modification and were subjected to the lithium naphthalenide reduction, to test the scope of the reaction and the compatibilities of various functional groups. The reduction products and side products were isolated and the results were rationalized.

I. Preparation of the lithium naphthalenide stock solution and test of its stability:

Chunks of solid lithium metal were cut into small pieces, which were washed with dry Skelly B, dried briefly with a stream of argon and added to a solution of naphthalene in THF. It took about a day at room temperature for the solid lithium metal to dissolve in the solution, yielding a dark blue solution. This solution was stored in the freezer at about -4 °C. During a one- to two-month period of time, no substantial loss of reactivity was observed. When quenched with water and extracted with ether, the stock solution gave only traces of side products. These side products usually did not hinder the separation of the desired products from the reduction mixtures obtained from the TMPDAs.

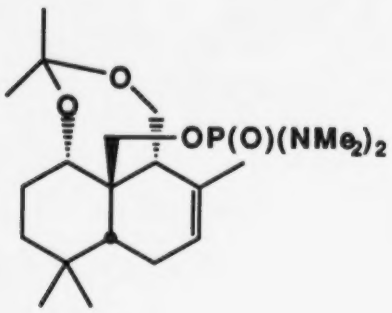
II. Preparation and reduction of the tetramethylphosphoro-diamidates:

A selected number of compounds with diverse functionalities were used as starting materials for the preparation of the TMPDAs. Our modification was

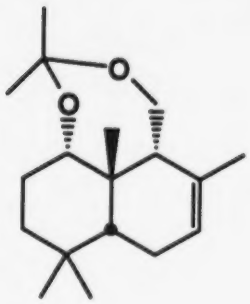
applied to sterically congested alcohols. For the less hindered ones, either Ireland's or our method was used. No efforts were not made to optimize the yields of the TMPDAs, since our main focus was to investigate the radical anion reduction.

The reduction of the TMPDAs was actually very straightforward. It simply involved the addition of the lithium naphthalenide solution *via* a syringe to a small reaction flask containing the TMPDA. The TMPDA would be dissolved and reduced at room temperature under argon. The reaction process could be monitored with thin-layer chromatography and it usually took 10-60 min, depending on the reactivity of the substrate, and the concentration of both the reagent and the substrate. The color of the reagent served as an indicator for itself. It should stay blue or bluish green if excess radical anion was present. If the starting material was still present but the color turned light green, brown or yellow, this was a good indication that more reagent was required. Work-up of the reaction could be easily done by addition of water to the reaction flask to quench the reaction followed by extraction with ether and subsequent washing, drying, filtration, concentration and column chromatography. If any functional group in the product(s) would be susceptible to reactions with the lithium hydroxide produced, a buffer solution, like saturated aqueous NH_4Cl or saturated aqueous KH_2PO_4 would be used in place of water. In all the cases we have investigated, no serious problem was encountered in the separation of the reduction product from naphthalene. The need for α-dimethylamino-naphthalene never arose.

Compound **1** was prepared from the corresponding neopentyl primary alcohol, as described in the previous chapter. In a test run, compound **1** was reduced with lithium naphthalenide solution to afford 60% of the reduced

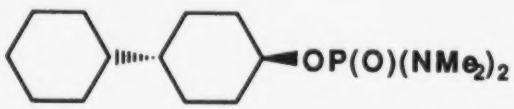


1



2

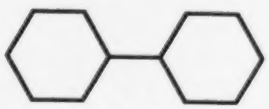
product, compound **2**, together with 12% of the corresponding alcohol and 13% of the unreacted starting material **1** (due to an insufficient amount of naphthalenide). Based on the amount of compound **1** actually consumed, the yield for compound **2** and the corresponding alcohol would be 70% and 14%, respectively.



3

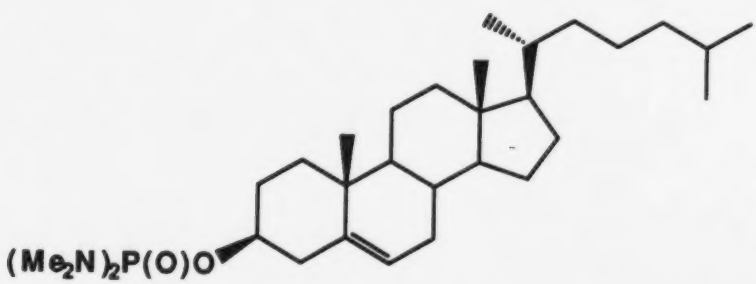
Compound **3** was prepared from *trans*-4-cyclohexylcyclohexanol in 65% yield using our method. This was one of the first runs done to test the quality of an old bottle of DMPADC. No effort was made to improve the yield. The ^{1}H NMR spectrum indicated the presence of the two dimethylamino groups, with a doublet at 2.61 ppm and the characteristic coupling constant $^{3}J_{P\text{-}H}$ of 9.8 Hz. The α-proton of the TMPDA group also gave a well defined splitting pattern of doublet of triplets of triplets, coupled with the neighboring equatorial and axial protons and the phosphorus atom. The methyl groups on nitrogen appeared as a doublet with a $^{2}J_{C\text{-}N\text{-}P}$ of 3.8 Hz at 36.56 ppm in the ^{13}C NMR APT spectrum. Coupling constants of 5.3 Hz and 4.5 Hz were also observed for the couplings

between P and the α– and β–carbons of the TMPDA group. The IR spectrum showed strong absorption bands at 1229, 1037 and 992 cm^{-1}, due to P=O, O-C and P-O stretching vibrations. High resolution mass spectrometry (HRMS) gave a molecular ion peak at 316.2279, consistent with the formula $C_{16}H_{33}N_2O_2P$ (calcd. 316.2280). The base peak appeared at 153.0791, suggesting a fragment of $C_4H_{14}O_2N_2P$ (calcd. 153.0793), which could be formed through a McLafferty type of rearrangement, followed by abstraction of another proton.



4

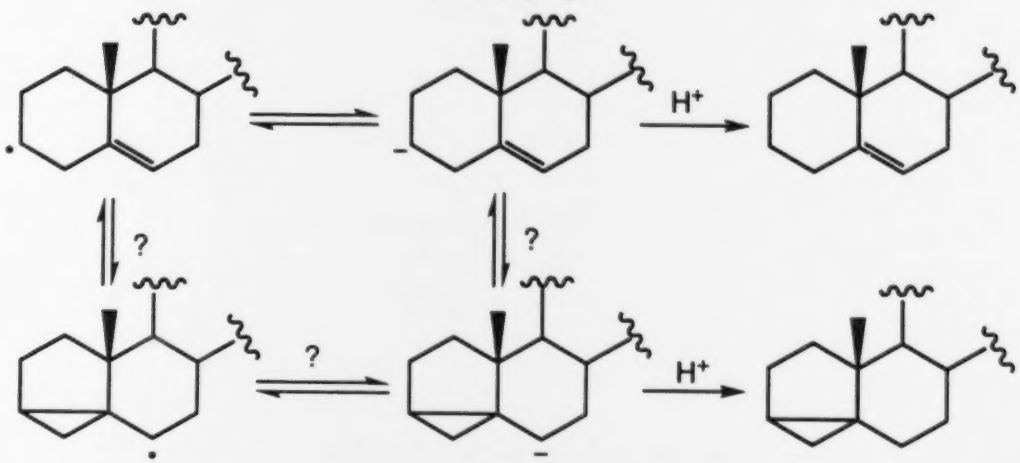
Compound **4** was obtained from the reduction of compound **3** in 66% yield. The low yield could be partially attributed to the volatility of the product whose bp was 99 - 100 °C at 9 torr. Its ^{13}C NMR APT resonances at 43.53, 30.25 and 26.96 ppm matched those reported in the literature.[59] The IR bands reported in the literature were also present in the IR spectrum of compound **4**. High resolution mass spectrometry gave the molecular ion at 166.1721 (calcd. for $C_{12}H_{22}$: 166.1722).



5

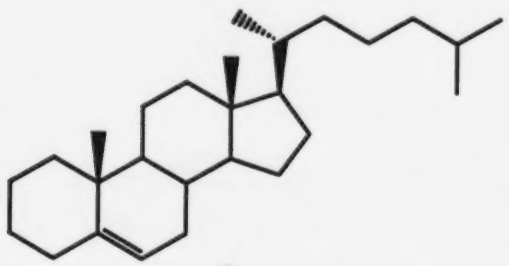
Cholesterol was chosen for its availability in our laboratory. Besides, we were also interested in seeing whether the Δ^5 double bond would interfere with the formation of the TMPDA, or the radical or anion formed from the reduction of the TMPDA with lithium naphthalenide (Scheme 3-4). It was known that, in Li-$EtNH_2$ reduction, the C=C double remained intact and no cyclopropyl ring formation was observed.[55]

Scheme 3-4



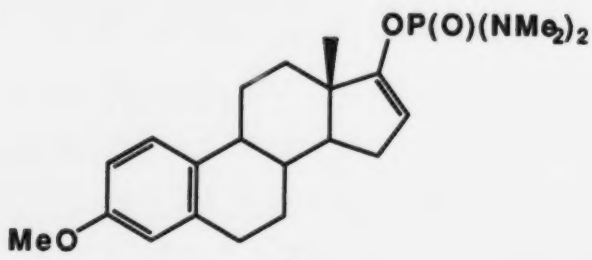
Compound **5** was obtained in 67% yield from crude cholesterol using our procedure. Its ^1H NMR spectrum gave the resonances for the olefinic proton and the α-proton of the TMPDA group at 5.36 and 4.12 ppm, respectively. The two dimethylamido groups gave two doublets at 2.63 and 2.62 ppm, each with a coupling constant of 9.9 Hz. In its ^{13}C NMR APT spectrum, the methyls on nitrogen, the α-carbon and the two β-carbons resonated at 36.60, 75.17, 40.31 and 29.87 ppm as doublets, with coupling constants of 3.0, 5.0, 5.0, 4.0 Hz, respectively, due to couplings with phosphorus atom. The IR spectrum gave strong absorption bands at 1229 and 993 cm^{-1}, due to the TMPDA group. High

resolution mass spectrometry gave the molecular ion M^+ at 520.4137 (calcd. for $C_{31}H_{57}N_2O_2P$: 520.4158). The base peak appeared at 153.0795 (calcd. for $C_4H_{14}O_2N_2P$: 153.0793) for the protonated McLafferty rearrangement product of the TMPDA group.



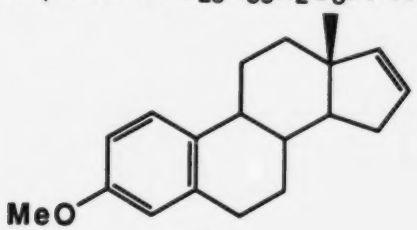
6

Compound **5** was reduced with a lithum naphthalenide stock solution. Two products were isolated. The first one was characterized as compound **6** (70%) and the more polar one as cholesterol (17%). No cyclopropyl ring containing compound was detected. The ^1H NMR spectrum of compound **6** showed the typical olefinic proton resonance at 5.27 ppm and carbon-13 resonances for the sp^2 carbons at 143.82 and 119.05 ppm. Both the ^{13}C NMR APT spectrum and melting point matched the reported values in the literature.[60] High resolution mass spectrometry gave the molecular ion peak at 370.3584 (calcd. for $C_{27}H_{46}$: 370.3600).



7

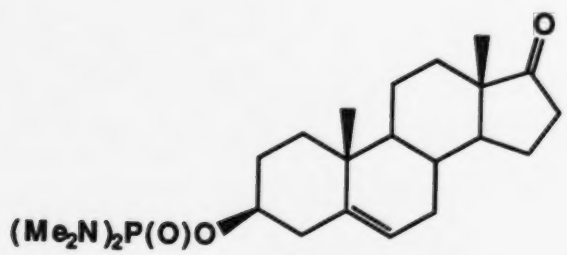
Compound **7** was prepared from the parent ketone compound, 3-methoxyestra-1,3,5(10)-trien-17-one in 64% yield by LDA deprotonation to form the enolate followed by phosphorylation with TMDAPC. Its ^{1}H NMR spectrum indicated the presence of a trisubstituted C=C double bond with resonance of the olefinic proton at 5.11 ppm. The four methyls of the two amido groups appeared at around 2.69 ppm as two sets of doublets, each with a coupling constant of 9.9 Hz. In ^{13}C NMR APT, the newly formed C=C double bond carbons appeared at 160.00 and 104.70 ppm as two doublets, due to couplings with the phosphorous atom. The coupling constant $^{3}J_{P-C}$ with the quaternary C-13 at 44.89 ppm was 6.0 Hz. The $^{2}J_{P-C}$ for the methyl groups on the two amido groups was 3.8 Hz. The band at 1624 cm^{-1} in the IR spectrum was typical of the C=C double bond of the enol ester. The two strong bands at 1237 and 987 cm^{-1} were due to the TMPDA group. High resolution mass spectrometry gave the molecular ion at 418.2389 (calcd. for $C_{23}H_{35}N_2O_3P$: 418.2385).



8

Compound **7** was subjected to lithium naphthalenide reduction. Two compounds were isolated, the first being compound **8** (73%) and the second one being the recovered keto compound (13%). The ^{1}H NMR of compound **8** indicated the formation of a *cis* disubstituted C=C bond, with two resonance signals at 5.91 and 5.74 ppm and a coupling constant of 5.7 Hz between them. The ^{13}C NMR spectrum had the C=C double bond carbons resonating at

144.05 and 129.30 ppm. High resolution mass spectrometry gave the molecular ion at 268.1526 (calcd. for $C_{19}H_{24}O$: 268.1867).



9

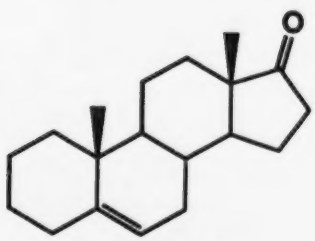
Stinnett *et al.* [33] reported that, when an aliphatic aldehyde or ketone possessing an α-hydrogen was treated with lithium naphthalenide, 18-59% of the carbonyl compound underwent deprotonation to afford the enolate, which was inert to reduction and was converted back to the ketone or aldehyde upon protonation. The other products were the mono- and dialkylated 1,4-dihydronaphthalenes (see Tables 3-1 and 3-2, and Scheme 3-2). With compound **9**, whose one side was blocked by the angular methyl group, would there be substantially less alkylated products and more deprotonation product? If this was the case, we would be able to selectively reduce the TMPDA group and keep the keto group. Another scenario would be that the TMPDA reacted at a much faster rate than the keto group. By controlling the temperature, we should be able to selectively reduce the TMPDA group. The third possibility was that the nucleophilic attack on the carbonyl was much faster than the deprotonation or the reduction of the TMPDA group. To test these possibilities, compound **9** was synthesized.

Compound **9** was prepared from 3β-hydroxy-5-androsten-17-one in 62% yield. The latter compound was first treated with *t*-BuLi at -78 °C to selectively deprotonate the hydroxy group. The resulting alkoxide was reacted with

tetramethyldiamidophosphorochloridate. In the ^{1}H NMR spectrum, the α-proton of the TMPDA group appeared at 4.12 ppm as a multiplet. The two dimethylamino groups appeared as two doublets at 2.63 and 2.62 ppm, each with a coupling constant of 9.9 Hz. In the ^{13}C NMR spectrum, the *N*-methyls, the α- and the two β-carbons appeared as doublets at 36.54, 74.90, 40.20 and 29.71 ppm, respectively, due to coupling with the phosphorous atom. The carbonyl carbon resonated at 220.89 ppm. The IR spectrum displayed the typical bands at 1739 cm^{-1} for the carbonyl group and at 1023, 1031, 991 and 981 cm^{-1} for the TMPDA group. High resolution mass spectrometry failed to give the molecular ion peak. However, the characteristic base peak of 153.0785 (calcd. for $C_4H_{14}N_2O_2P$: 153.0793) indicated the presence of the TMPDA group. Chemical ionization mass spectrometry gave 423.4 as the M^+ + 1 peak.

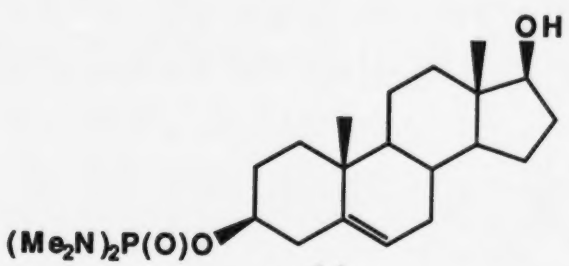
Compound **9** was subjected to the radical anion reduction and the reaction was monitored at different time intervals. Thin-layer chromatography analysis indicated that the deprotonation and nucleophilic attack proceeded at comparable rates, while the reduction of the TMPDA group was much slower than the first two reactions. Obviously, the ketone group would not survive under this direct reduction condition.

Another attempt was made by deprotonating the ketone first with LDA, followed by radical anion reduction. Because of the presence of diisopropylamine, a large amount of lithium naphthalenide was consumed. The reaction was very messy and no major product was formed. Another way of deprotonating the ketone was to use hydrides, such as KH, as the base. Compound **10** was indeed produced, but only in poor yield.



10

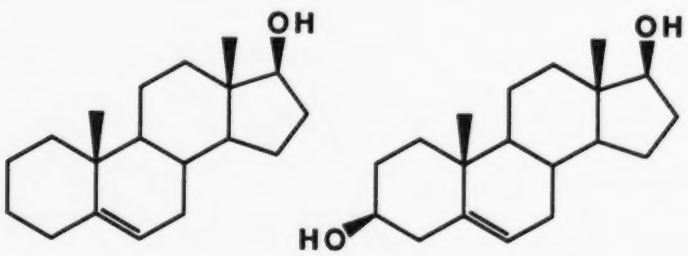
Another way to protect a ketone group would be to reduce it to an alcohol and to oxidize it back after the radical anion reduction of the TMPDA group. When a proton source, like a hydroxy group, and an aromatic ring were present at the same time, Ireland's reduction condition could not be applied, since Birch reduction of the aromatic ring would happen, at least to some extent.[55] With lithium naphthalenide, this would never happen, since the fastest reaction would be the deprotonation reaction, before anything else could happen. To test this, compound **11** was prepared from compound **9** by $NaBH_4$ reduction of the ketone group in isopropyl alcohol.



11

The reduction of the 17-keto group gave mainly the β-alcohol (>95%), which was consistent with literature reports.[61] The crude product, which was free of other impurities, was further purified by recrystallization to give pure compound **11**. In the ^1H NMR spectrum, the α-proton of the hydroxy group appeared at 3.62 ppm as a broad pseudo triplet with J = 7.6 Hz. The TMPDA

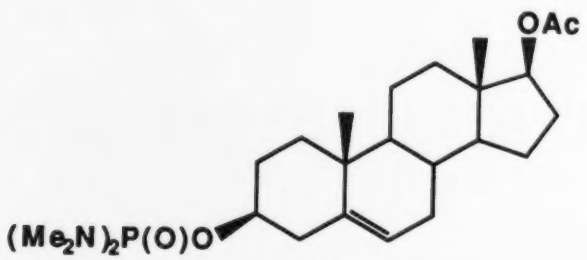
group remained intact, giving two doublets at 2.61 and 2.60 ppm, each with a coupling constant of 9.9 Hz resulting from coupling with P. Its ^{13}C NMR spectrum gave an antiphase signal at 81.86 ppm for the carbon bearing the hydroxy group. The doublets at 36.62, 75.20, 40.32 and 29.87 ppm were due to the *N*-methyls, the α- and the two β-carbons of the TMPDA group. The characteristic band for the hydroxy group appeared at 3362 cm^{-1} in its IR spectrum. Chemical ionization mass spectrometry gave the $M^+ + 1$ peak at 425.5. The molecular ion peak could not be observed in high resolution mass spectrometry. But the characteristic base peak of 153.0798 (calcd. for $C_4H_{14}N_2O_2P$: 153.0793) indicated the presence of the TMPDA group.



12 **13**

Compound **11** was subjected to lithium naphthalenide reduction. Due to the presence of the hydroxy group, two more equivalents of the reagent were needed due to its conversion to the alkoxide. Two compounds were isolated. The first one, compound **12**, was isolated in 75% yield. It resulted from direct reduction of the TMPDA group. The second one, compound **13**, a 3β,17β-diol, was isolated in 8% yield. It was derived from the cleavage of the TMPDA group by the P-O bond. In the ^1H NMR spectrum of compound **12**, the α-proton of the hydroxyl group at C-17 appeared at 3.63 ppm as a doublet of doublets. The olefinic proton resonated at 5.25 ppm as a broad doublet. In its ^{13}C NMR

spectrum, only three peaks appeared in the low field at 143.91, 118.71 and 82.04 ppm, due to the two sp^2-hybridized carbons and the α-carbon of the hydroxy group. The hydroxy group gave rise to the strong, broad band at 3253 cm^{-1} in the IR spectrum. High resolution mass spectrometry gave the molecular ion at 274.2299 (calcd. for $C_{19}H_{30}O$: 274.2297). Compound **13**, a diol, gave a doublet of doublets at 3.63 ppm, a multiplet at 3.50 ppm and a broad doublet at 5.33 ppm in the ^1H NMR spectrum, due to the α-protons of the 17β– and 3β-hydroxy groups and the olefinic proton. The carbons bearing the hydroxy groups appeared at 81.11 and 70.94 ppm in its ^{13}C NMR spectrum. In the IR spectrum, three strong bands at 3472, 3374 and 3210 cm^{-1}, due to the intermolecular hydrogen-bondings, illustrated the polyhydroxy nature of this compound. High resolution mass spectrometry gave the molecular ion at 290.2254 (calcd. for $C_{19}H_{30}O_2$: 290.2246).

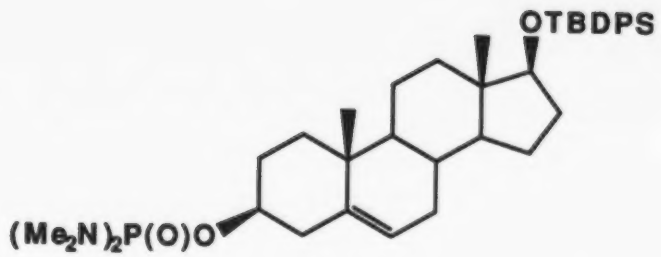


14

At this point, we decided to test the compatibilities of a few selected functional groups. The first one that came to our mind was an ester group, because of the uncertainty that existed around it. Vora and Holy showed that when an aliphatic ester with at least one α-hydrogen atom was treated with the naphthalenide radical anion, the major portion of the ester underwent the deprotonation reaction, which could be regenerated upon treatment with a proton source.[35] The other products were from the acylations of the 1,4-

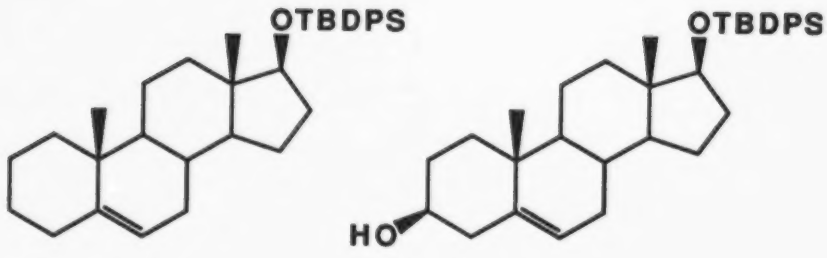
dihydronaphthalene. With compound **14**, where the ester group was blocked on one side by the methyl group, we would expect to have less nucleophilic attack of the radical anion on the carbonyl group, leading to the acylation products, and more deprotonation reactions, which would eventually give back the ester group. Compound **14** was prepared in 98% yield by treating compound **11** with acetic anhydride in pyridine. In the ^{1}H NMR spectrum, the hydrogen on C-17, which was now α- to an acetoxy group, experienced a downfield shift from 3.62 ppm, as in compound **11**, to 4.57 ppm. The CH_3 of the acetyl group appeared at 2.01 ppm as a singlet. The methyl groups of the amido groups remained at 2.61 and 2.60 ppm as two doublets. In the ^{13}C NMR spectrum, the carbonyl carbon and C-17 bearing the acetoxy group appeared at 171.23 and 82.81 ppm, respectively. The doublets at 36.57, 75.30, 40.23 and 29.79 ppm were due to the *N*-methyls, the α- and the two β-carbons of the TMPDA group. In its IR spectrum, the presence of the ester group was confirmed by the strong C=O stretching band at 1734 cm^{-1}. High resolution mass spectrometry failed to offer the M^+ ion peak. The base peak at 153.0799 again confirmed the presence of the TMPDA group. Chemical ionization mass spectrometry gave the $M^+ + 1$ peak at 467.3.

Compound **14** was treated with lithium naphthalenide at room temperature. It was found that the acetyl group was removed at a much faster rate than the TMPDA group, giving rise to compound **11**. After 1 hr when the reduction of the TMPDA was complete, the reaction was quenched with saturated aqueous NH_4Cl. No acetyl group (the methyl at around 2.0 ppm) could be found in the ^{1}H NMR spectrum of the crude mixture. This clearly implied that ester groups were not compatible with the reaction conditions.



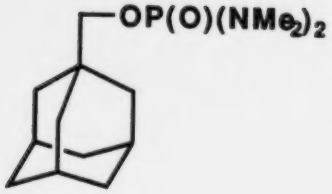
15

Another attempt was made with silyl ethers as the protecting groups for the hydroxy group. These groups were labile, to a certain extent, to hydroxide and/or alkoxides. It was almost inevitable to have traces of hydroxide in the lithium naphthalenide solution, since it might be carried over from the lithium metal, or produced from trace amounts of water from the metal, solvent, the substrate or the glassware. Alkoxides were also generated during the reduction of the TMPDA group, since this group could also be cleaved by the P-O bond, as noted previously. The effect of the radical anion on the silyl ether was also unclear at this point. For this purpose, compound **15** was prepared by silylation of compound **11** with *t*-butyldiphenylsilyl chloride (TBDPSCl) in 95% yield. The presence of the silyl group was demonstrated in its ^{1}H NMR spectrum by the multiplets at around 7.63 ppm (4H) and 7.35 ppm (6H), due to the two phenyl groups, and a singlet at 1.05 ppm for the *tert*-butyl group. The TMPDA group manifested itself by the two doublets at 2.61 and 2.60 ppm, with 6 protons each. In the ^{13}C NMR spectrum, eight more lines between 140 - 120 ppm indicated the presence of the TBDPS group. The four doublets at 36.57, 75.15, 40.27 and 29.83 ppm were due to the *N*-methyls, the α- and the two β-carbons of the TMPDA group. The M^{+} + 1 ion peak appeared at 663.5 in chemical ionization mass spectrometry.



16 **17**

Lithium naphthalenide reduction of compound **15** afforded two products. The less polar one, compound **16**, resulted from the removal of the TMPDA group in 67% yield. The more polar one, compound **17**, due to the P-O bond cleavage of the TMPDA group, was isolated in 9% yield. For compound **16**, the TBDPS group survived, as evidenced by the multiplets at 7.65 and 7.34 ppm due to the two phenyl groups and the singlet at 1.06 ppm due to the *tert*-butyl group. In the ^{13}C NMR spectrum, eight more lines between 145 and 115 ppm, due to the two diastereotopic phenyl groups, and the one at 82.63 ppm, due to the carbon α- to the oxygen, illustrated the presence of the silyl ether. High resolution mass spectrometry gave the molecular ion at 512.3475 (calcd. for $C_{35}H_{48}OSi$: 512.3475). Compound **17** differed from compound **16** by the presence of the 3β-hydroxy group. This was shown by the extra resonance signal at 3.46 ppm as a multiplet in the ^{1}H NMR spectrum and an antiphase line at 71.81 ppm in the ^{13}C NMR spectrum. The IR spectrum gave a broad, strong band at 3346 cm^{-1}, characteristic of a hydroxy group. High resolution mass spectrometry had the molecular ion peak at 527.3321 (calcd. for $C_{35}H_{47}O_2Si$: 527.3345).



18

Compound **18** was prepared from adamantylmethanol in 78% yield using Ireland's protocol. This compound was highly symmetrical. In the ^{1}H NMR spectrum, the methylene group α- to the TMPDA group appeared at 3.42 ppm as a doublet with $^{3}J_{P-H}$ = 4.4 Hz. The 12 hydrogens from the *N*-methyls resonated at 2.62 ppm with $^{3}J_{P-H}$ = 9.6 Hz. In the ^{13}C NMR spectrum, the *N*-methyls, the methylene α- to the TMPDA group and the quaternary carbon β- to it appeared at 36.69, 74.52 and 33.91 ppm, respectively, all as doublets due to couplings with the phosphorus atom. The IR spectrum gave strong bands at 1260 and 942 cm^{-1} due to the TMPDA group. High resolution mass spectrometry gave the molecular ion peak at 300.1963 (calcd. for $C_{15}H_{29}N_2O_2P$: 300.1966). The reduction of this compound was straightforward as with the others. But since the product was prone to sublimation, the yield was low. Compound **18** was used mainly for the trapping experiments, which are described in the next section.

III. Attempts to trap the carbanion generated by the reduction of TMPDAs.

There were numerous reports of successful trapping experiments of the carbanions produced by the arenide radical anion reductions in the literature. In those experiments, the reductions to generate the carbanions were usually

carried out at low temperatures, mostly -78 °C. The electrophile was added after the reduction was complete and the trapping was carried out at the same temperature. In cases where the trapping was slow, the reaction mixture was allowed to warm up, sometimes to room temperature. Sometimes, when the first step, the radical anion reduction, was easy and fast, the trapping reagent could be mixed with the substrate prior to the addition of the reducing agent. All these were possible only when the carbanion was sufficiently stable under the conditions by which it was produced.

In Ireland's protocol, the carbanions produced would react instantly with the solvent to abstract a proton, since the carbanions were much stronger bases than amide or *N*-ethylamide. Furthermore, because the solvent, liquid ammonia or ethylamine, itself was a good nucleophile in large excess, any electrophile added would probably be consumed by the solvent before it had a chance to react with the carbanion. Due to the above two reasons, it would be impossible to trap the carbanions produced by the reduction of the TMPDA groups.

With lithium naphthalenide, the solvent was not nucleophilic. The excess of the reducing reagent, which would also reduce the trapping agents, was very limited. We would expect the trapping to be feasible.

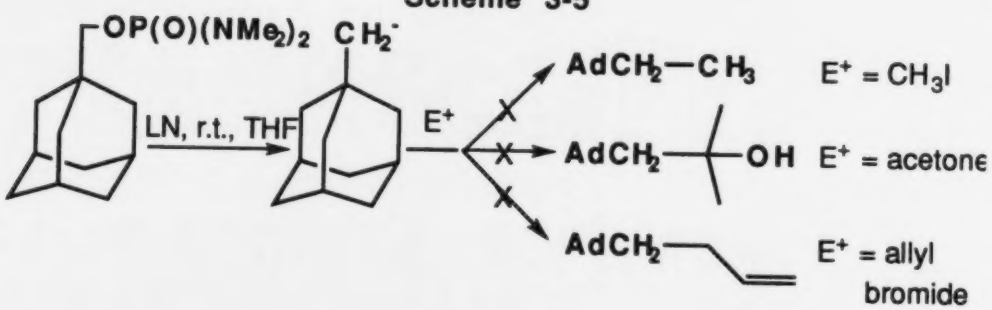
The TMPDA group, as shown earlier, was extremely stable under various reaction conditions. Even with lithium naphthalenide, the reaction was slow, as compared with the reductions of the halide and those sulfur derived functional groups. At room temperature, the reduction of TMPDA groups usually took 5-30 min to complete. Another set of runs done with compound **18** at different temperatures indicated that this reaction virtually did not occur below -20 °C.

A few runs of the trapping experiment were done with compound **18**. The electrophiles applied were very reactive ones, namely, methyl iodide,

acetone and allyl bromide.[62] They were known for sure to be reactive at room temperature.

Compound **18** was reduced at room temperature with lithium naphthalenide. After the reduction was complete, an excess of trapping agent (usually 10-20 eq.) was added at room temperature. The bluish color of the radical anion disappeared instantly, since the reductions of these reagents were very fast, which consumed the excess radical anion right away. The reaction mixture was stirred at room temperature for another period of time, and monitored with thin-layer chromatography. Finally, the reaction was worked-up and the crude mixture was analyzed with thin-layer chromatography and high resolution NMR spectroscopy. Surprisingly, no desired product was ever found (Scheme 3-5). When the reduction reactions were done at 0 °C, the results were the same.

Scheme 3-5



These results prompted us to search for answers to explain them and hopefully to find ways to solve or get around this problem. After comparing our reaction conditions with the ones reported in the literature, the major differences we found were the reaction temperatures.

Carbanions of simple sp^3-hybridized carbons are the strongest bases. The pK_as of their conjugate acids, C-H, are around 50. For alkenes and

aromatic compounds, where the carbons are sp^2-hybridized, the relative acidities are much higher. The pK_as are around 43. This difference of 10^7 times in acidity may not be significant at low temperatures, due to kinetic factors. At around room temperature, this may not be the same again. What happened in our trapping experiments could be that the carbanions generated underwent a rapid proton exchange reaction with naphthalene to become protonated, even before the trapping agents were added. They never had a chance to react with the electrophiles.

Since the reductions were slow at lower temperatures, they had to be run at around room temperature. Under these conditions, the carbanions produced had very short life times. The trapping of the carbanions produced this way was doomed to fail.

IV. Conclusions:

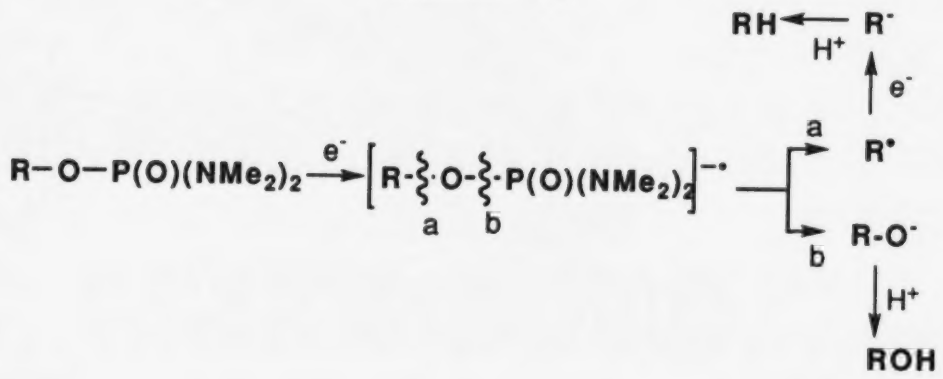
The reduction of TMPDA group was made really easy. It simply involved the addition of a stock solution of lithium naphthalenide to the substrate and subsequent stirring at room temperature for a short period of time. Work-up of the reaction was also very straightforward: water was adde to the reaction mixture at room temperature and then extracted with ether. Column separation of the products from a large amount of naphthalene sometimes posed a challenge. But it never became a serious problem to us. Should the R_f value of the product be really close to that of naphthalene and the two become inseparable by chromatography, substitution of naphthalene with α-dimethylaminonaphthalene would be the answer.

A number of runs with different substrates had demonstrated the compatibilities of this set of reaction conditions with some functional groups.

The presence of those easily reducible functional groups, like halides, sulfones, sulfoxides, *etc.*, were definitely not suitable, because they would be reduced at much faster rates than the TMPDA group. Ketones, aldehydes and esters, despite their tendency to form enolates to a certain extent, were not suitable for synthetic purposes. Non-conjugated C=C double bonds, aromatic rings, ethers, silyl ethers, acetals and hydroxy group could survive the reaction conditions.

It is noteworthy that, like the reduction with lithium in ethylamine, the bond cleavage could happen at either the C-O σ-bond or the P-O σ-bond (Scheme 3-6). In the former case, the desired reduction product would be afforded, while in the latter case, the corresponding alcohol would be recovered. The formation of alcohol usually accounted for around 10% of the reaction.

Scheme 3-6



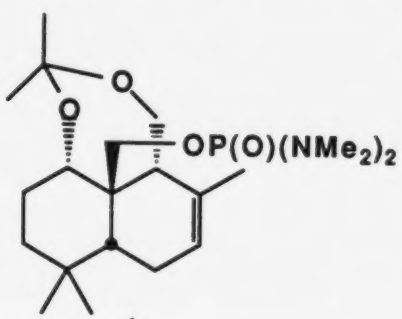
Trapping of the carbanions produced from the reduction of TMPDA derivatives was not feasible, due to their rapid proton exchange with naphthalene.

Experimental

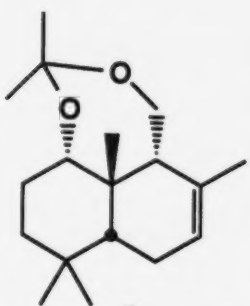
General and Materials

Refer to Chapter 1, Experimental section for a detailed description.

(1R*,5R*,9S*,14S*)-2,6,6,11,11-Pentamethyl-14-*N,N,N',N'*-tetramethyldiamidophosphoroxymethyl-10,12-dioxatricyclo-[7.4.1.0^{5,14}]tetradec-2-ene (1) and (1R*,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxa-tricyclo[7.4.1.0^{5,14}]-tetradec-2-ene (2)



1



2

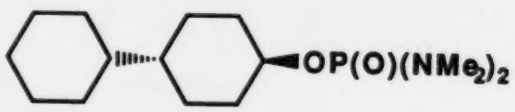
For the preparation and spectral data of compound **1** and compound **2**, please refer to compound **225** and compound **204**, respectively, in chapter 2.

In Chapter 2, compound **2** was prepared by reducing compound **1** with lithium in ethylamine at 0 °C. The reduction of compound **1** with lithium naphthalenide is discussed here.

A lithium naphthalenide solution (0.656 M, 6 mL, 4 mmol) was added to a solution of compound **1** (0.379 g, 1.01 mmol) in THF (1 mL). The bluish reaction mixture was stirred at room temperature for 30 min. Water (1 mL) was

added and the resulting mixture was extracted with ether (3 x 20 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash chromatography of the residue on silica gel with Skelly B afforded compound **2** (167 mg, 0.601 mmol, 60%, 69% based on the consumed starting material). Further elution with acetone and Skelly B (1 : 10 to 1 : 6) afforded the corresponding alcohol (34 mg, 0.12 mmol, 12%) and the starting material **1** (50 mg, 0.13 mmol, 13%).

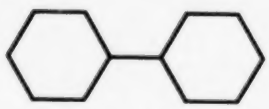
trans-4-Cyclohexyl-1-_N,N,N'N'_-tetramethyldiamidophosphoroxy-cyclohexane (3)



trans-4-Cyclohexycyclohexanol (73 mg, 0.40 mmol) was dissolved in DME - TMEDA (4 : 1, 1.2 mL) under argon. While chilled with an ice bath, *n*-BuLi in hexanes (1.6 M, 0.38 mL, 0.61 mmol) was added dropwise. The resulting solution was stirred at room temperature for 15 min before DMPADC (0.32 g, 2 mmol) was added. The reaction mixture was stirred at room temperature for 5 hr under argon. It was cooled to 0 °C and anhydrous dimethylamine (1 mL) was added. Stirring was continued for 20 min at 0 °C. The reaction mixture was poured into ice water and extracted with ether (2 x 20 mL). The extracts were washed three times with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with ethyl acetate - Skelly B (1 : 3) afforded compound **3** (86 mg, 0.27 mmol, 68%): mp 34.5 - 36.0 °C; IR ($CDCl_3$, cast): 1229 (st, P=O), 1037 cm^{-1} (st, P-O or C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 4.13

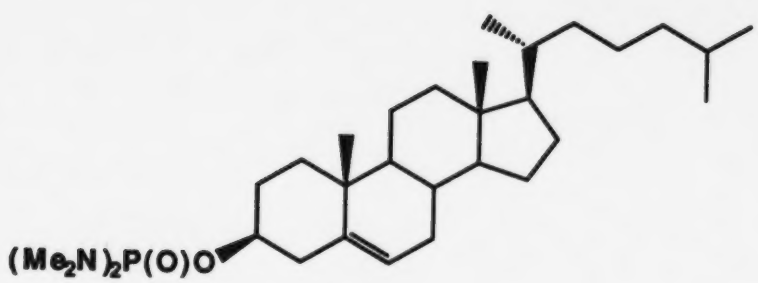
(dtt, $J_1 = J_2 = 7.3$ Hz, $J_3 = 5.5$ Hz, 1H, POCH), 2.61 (d, J = 9.8 Hz, 12H, $PNCH_3$), 2.05 (m, 2H), 1.67 (m, 7H), 1.34 (m, 2H), 1.34 (m, 2H), 1.3 - 0.8 (m, 9H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 75.13 (d, J = 5.3 Hz, ap), 42.63 (ap), 42.21 (ap), 36.56 (d, J = 3.8 Hz, ap), 34.03 (d, J = 4.5 Hz, p), 33.97 (p), 30.34 (p), 27.88 (p), 26.77 (p); HRMS: 316.2279 (M^+, calcd. for $C_{16}H_{33}N_2O_2P$: 316.2280), 153.0791 (base peak, calcd. for $C_4H_{14}O_2N_2P$: 153.0793).

Bicyclohexyl (4)



A lithium naphthalenide solution (0.66 M, 1.0 mL, 0.66 mmol) was added to compound **3** (58.8 mg, 0.189 mmol). The resulting blue reaction mixture was stirred at room temperature for 30 min. Water (3 mL) was added and it was extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with Skelly B afforded compound **4** (20.80 mg, 0.125 mmol, 66%): IR ($CDCl_3$, cast): 2922 (st, C-H stretching), 2851 (st, C-H stretching), 1448 cm^{-1} (m, C-H bending); ^1H NMR (360 MHz, $CDCl_3$): δ 1.78-1.60 (m, 8H), 1.38 -0.82 (m, 14H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 43.53 (ap), 30.25 (p), 26.96 (p, two carbon signals overlapping); HRMS M^+: 166.1721 (calcd. for $C_{12}H_{22}$: 166.1722).

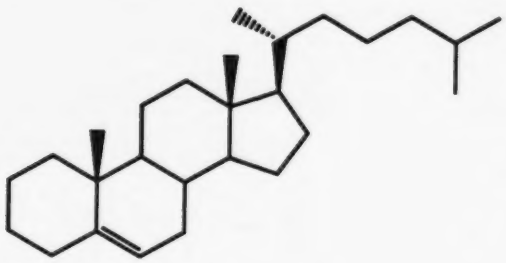
3β-*N,N,N'N'*-Tetramethyldiamidophosphoroxy-5-cholestene (5)



A solution of *n*-BuLi in hexanes (1.6 M, 2.1 mL, 3.4 mmol) was slowly added to a solution of cholesterol (0.882g, 2.28 mmol) in DME-TMEDA (4 : 1, 10 mL) and the resulting reaction mixture was stirred at room temperature for 30 min before DMPADC (1.26 ml, 11.4 mmol) was slowly added. Stirring was continued at room temperature for another 10 hr. The reaction mixture was cooled to 0 °C with an ice-bath and dimethylamine (6 mL) was added. After stirring for 30 min, the reaction mixture was poured into water and extracted with ether. The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel with acetone-Skelly B (1 : 6) to afford compound **5** (0.790 g, 1.52 mmol, 67%). Recrystallization from ether-Skelly B gave white crystals: mp 136.5-137.5 °C; IR ($CDCl_3$, cast): 1229 (st, P=O), 993 cm^{-1} (st, P-O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.36 (br d, J = 4.6 Hz, 1H, C=C**H**), 4.12 (m, 1H, POC**H**), 2.63 (d, J = 9.9 Hz, 6H, PNC**H**$_3$), 2.62 (d, J = 9.9 Hz, 6H, PNC**H**$_3$), 2.37 (d, J = 7.7 Hz, 2H), 1.97 (m, 3H, 1.82 (m, 2H), 1.7 - 0.9 (m, 22H), 1.00 (s, 3H, C**H**$_3$), 0.90 (d, J = 6.6 Hz, 3H, CHC**H**$_3$), 0.86 (d, J = 6.6 Hz, 3H, CH_2CHCH_3), 0.85 (d, J = 6.6 Hz, 3H, CH_2CHCH_3), 0.66 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 139.84 (p), 122.58 (ap), 75.17 (d, J = 5.0 Hz, ap), 56.70 (ap), 56.18 (ap), 50.07 (ap), 42.35 (p), 40.31 (d, J = 5.0 Hz, p), 39.77 (p), 39.55 (p), 37.03 (p), 36.60 (d, J = 3.0 Hz, ap), 36.49 (p), 36.22 (p), 35.82 (ap), 31.93 (p), 31.89 (ap), 29.87 (d, J = 4.0 Hz, p), 28.25 (p), 28.03 (ap), 24.31 (p), 23.86

(p), 22.83 (ap), 22.58 (ap), 21.08 (p), 19.36 (ap), 18.74 (ap), 11.88 (ap); HRMS: 520.4137 (M^+, calcd. for $C_{31}H_{57}N_2O_2P$: 520.4158), 153.0795 (base peak, calcd. for $C_4H_{14}O_2N_2P$: 153.0793). Anal. calcd. for $C_{31}H_{57}N_2O_2P$: C 71.5%, H 11.03%, N 5.38%; found: C 71.4%, H 10.91%, N 5.39%.

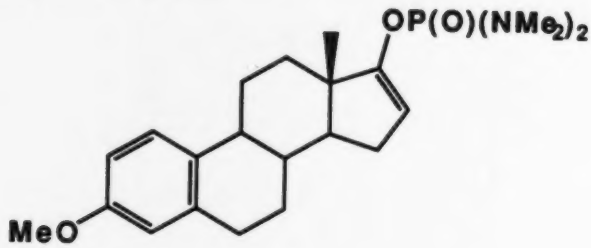
5-Cholestene (6)



A lithium naphthalenide solution (0.66 M, 2.4 mL, 1.6 mmol) was added to compound **5** (196 mg, 0.376 mmol). The resulting reaction mixture was stirred at room temperature under argon for 30 min. Water (10 mL) was added and it was extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Flash column chromatography of the residue on silica gel with 100% Skelly B gave compound **6** (97.45 mg, 70%). Further gradient elution with acetone-Skelly B (0 : 100 to 1 : 3) gave cholesterol (43.91 mg, 17%). Compound **6** was recrystallized from ether-Skelly B to give white crystals: mp 91.0 - 92.0 °C; IR ($CDCl_3$, cast): 2932 cm^{-1} (st, br, C-H stretching); ^1H NMR (360 MHz, $CDCl_3$): δ 5.27 (m, 1H, C=C**H**), 2.25 (m, 1H), 1.98 (m, 3H), 1.82 (m, 2H), 1.72 (m, 1H), 1.6 - 0.9 (m, 23H), 0.99 (s, 3H, CH_3), 0.91 (d, J = 6.5 Hz, 3H, CHCHC**H**$_3$), 0.86 (d, J = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$), 0.86 (d, J = 6.6 Hz, 3H, CH_2CHMe_2), 0.67 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 143.82 (p), 119.05 (ap), 56.98 (ap),

56.27 (ap), 50.70 (ap), 42.39 (p), 39.97 (p), 39.61 (p), 37.62 (p), 36.29 (p), 35.88 (ap), 32.98, (p), 31.98 (p), 31.93 (ap), 28.32 (p), 28.15 (p), 28.09 (ap), 24.36 (p), 23.91 (p), 22.88 (ap), 22.64 (p), 22.63 (ap), 20.85 (p), 19.54 (ap), 18.80 (ap), 11.95 (ap); HRMS M+: 370.3584 (calcd. for $C_{27}H_{46}$: 370.3600). Anal. calcd. for $C_{27}H_{46}$: C 87.48%, H 12.57%; found: C 87.03%, H 12.25%.

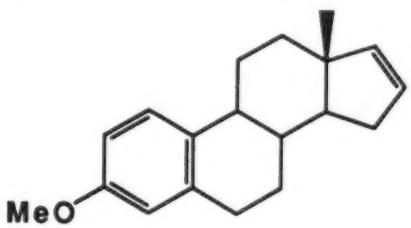
3-Methoxy-*N,N,N'N'*-tetramethyldiamidophosphoroxyestra-1,3,5(10),16-tetraene (7)



n-BuLi in hexanes (1.6 M, 0.33 mL, 0.53 mmol) was slowly added to a solution of diisopropylamine (0.73 mL, 0.53 mmol) in THF (2 mL) at -78 °C. The reaction mixture was allowed to warm up to room temperature and stirring was continued for another 20 min. It was cooled to -78 °C again. A solution of 3-methoxyestra-1,3,5(10)-trien-17-one (123.4 mg, 0.434 mmol) in DME - TMEDA (4 : 1, 3 mL) was added and stirring was continued for another 30 min before tetramethyldiamidophosphorochloridate (90%, 0.21 mL, 1.30 mmol) was added. The reaction mixture was stirred at room temperature under argon for 2 days. Water (10 mL) was added and the resulting mixture was extracted with ether (3 x 15 mL). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. Flash chromatography of the residue with acetone - Skelly B (1 : 20 to 1 : 6) gave the recovered starting material (21.02 mg, 17%) and compound **7** (116.55 mg, 0.31 mmol, 64%).

Compound **7**: mp 100.5 - 101.5 °C; IR (CH_2Cl_2, cast): 1624 (md, C=C of enol ester); 1237 (st, P=O), 987 cm^{-1} (st, P-O); ^1H NMR (360 MHz, $CDCl_3$): δ 7.15 (d, J = 8.6 Hz, 1H, C_1 - **H**), 6.68 (dd, J_1 = 8.6 Hz, J_2 = 2.8 Hz, 1H, C_2 - **H**), 6.61 (d, J = 2.8 Hz, 1H, C_4 - **H**), 5.11 (m, 1H, C_{16} - **H**), 3.75 (s, 3H, OCH_3), 2.87 (m, 2H), 2.69 (d, J = 9.9 Hz, 6H, $PNCH_3$), 2.69 (d, J = 9.9 Hz, 6H, $PNCH_3$), 2.35 (m, 3H), 2.0 - 1.3 (m, 8H), 0.92 (s, 3H, C_{13} - CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 160.00 (d, J = 8.3 Hz, p), 157.53 (p), 138.02 (p), 132.86 (p), 125.97 (ap), 113.90 (ap), 111.47 (ap), 104.70 (d, J = 3.0 Hz, ap), 55.24 (ap), 53.77 (ap), 44.89 (d, J = 6.0 Hz, p), 44.49 (ap), 37.01 (ap), 36.71 (d, J = 3.8 Hz, ap), 33.45 (p), 29.67 (p), 28.48 (p), 27.04 (p), 26.20 (p), 15.63 (ap); HRMS M^+: 418.2389 (calcd. for $C_{23}H_{35}N_2O_3P$: 418.2385). Anal. calcd. for $C_{23}H_{35}N_2O_3P$: C 66.01%, H 8.43%, N 6.69%; found: C 66.08%, H 8.49%, N 6.99%.

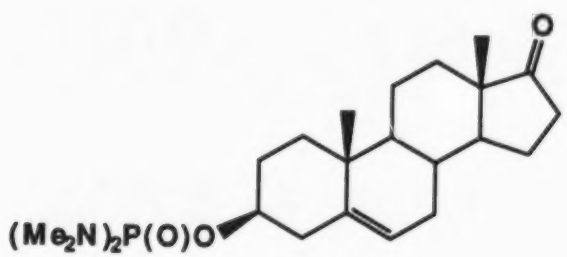
3-Methoxyestra-1,3,5(10),16-tetraene (8)



A lithium naphthalenide solution (0.66 M, 1.0 mL, 0.66 mmol) was added to compound **7** (66.75 mg, 0.159 mmol). The bluish reaction mixture was stirred at room temperature for 30 min under argon. Water (3 mL) was added and the resulting mixture was extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. Gradient flash chromatography of the residue with acetone : Skelly B (0 : 0 to 1 : 10) gave compound **8** (31.22 mg, 0.116 mmol, 73%) and

3-methoxyestra-1,3,5(10)-trien-17-one (5.95 mg, 0.021 mmol, 13%). Compound **8**: IR ($CDCl_3$, cast): 1609 (st, aromatic ring skeleton), 1575 (st, aromatic ring skeleton) and 1500 cm^{-1} (st, aromatic ring skeleton); ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 8.6 Hz, 1H, C_1 - **H**), 6.71 (dd, J_1 = 8.6 Hz, J_2 = 2.8 Hz, 1H, C_2 - **H**), 6.64 (d, J = 2.8 Hz, 1H, C_4 - **H**), 5.91 (ddd, J_1 = 5.7 Hz, J_2 = 2.4 Hz, J_3 = 1.0 Hz, 1H, C**H**=CHCH$_2$), 5.74 (ddd, J_1 = 5.7 Hz, J_2 = 3.0 Hz, J_3 = 1.5 Hz, 1H, CH=C**H**CH$_2$), 3.77 (s, 3H, OC**H**$_3$), 2.9 - 1.4 (m, 13H), 0.78 (s, 3H, C_{13} - C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 157.49 (p), 144.05 (ap), 138.03 (p), 133.20 (p), 129.30 (ap), 126.06 (ap), 113.92 (ap), 111.43 (ap), 55.48 (ap), 55.25 (ap), 45.85 (p), 44.65 (ap), 37.45 (ap), 35.99 (p), 31.83 (p), 29.84 (p), 28.05 (p), 26.67 (p), 17.14 (ap); HRMS M^+: 268.1526 (calcd. for $C_{19}H_{24}O$: 268.1867). Anal. calcd. for $C_{19}H_{24}O$: C 74.2%, H 10.97%; found: C 74.14%, H 11.07%.

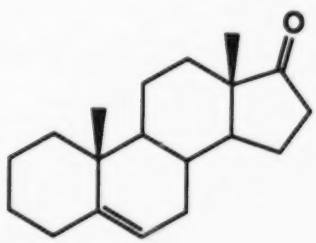
3β-*N,N,N'N'*-Tetramethyldiamidophosphoroxy-5-androsten-17-one (9)



Sodium hydride (60% dispersion in mineral oil, 0.305 g, 7.6 mmol) was mixed with DME - TMEDA (4 : 1, 5 mL). The resulting suspension was stirred at room temperature for 5 min before a solution of 3β-hydroxy-5-androsten-17-one (1.444 g, 4.75 mmol) in the same solvent mixture (5 mL) was added. The reaction mixture was stirred at room temperature for 20 min. *N,N,N',N'*-Tetramethyldiamidophosphorochloridate (90%, 2.5 mL, 15.2 mmol) was added

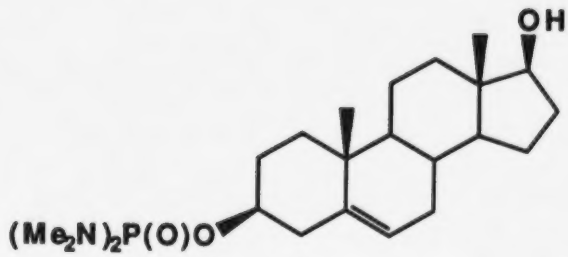
and the reaction mixture were stirred at room temperature under argon for 2 days. It was cooled with an ice-bath and a few drops of water was slowly added to destroy excess NaH. After 5 min, more water (20 mL) was added and the resulting mixture was extracted with ether (3 x 30 mL). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with acetone-Skelly B (1 : 6) afforded compound **9** (1.320 g, 8.6 mmol, 62%): mp 156.5 - 157.0 °C; IR (CH_2Cl_2, cast): 1739 (st, carbonyl), 1223 (st, P=O), 1031 (st, P-O), 991 cm^{-1} (st, P-O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.41 (br d, J = 4.6 Hz, 1H, C=C**H**), 4.14 (m, 1H, POC**H**), 2.65 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.64 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.6-0.9 (m), 1.05 (s, 3H, C**H**$_3$), 0.89 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 220.89 (p), 140.05 (p), 121.74 (ap), 74.90 (d, J = 4.8 Hz, ap), 51.66 (ap), 50.13 (ap), 47.47 (p), 40.20 (d, J = 4.2 Hz, p), 36.90 (p), 36.65 (p), 36.54 (d, J = 3.9 Hz, ap), 35.80 (p), 31.45 (ap), 31.38 (p), 30.73 (p), 29.71 (d, J = 4.0 Hz, p), 21.84 (p), 20.30 (p), 19.33 (ap), 13.50 (ap); CIMS: 423.4 (M^+ + 1); HRMS: 153.07849 (base peak, calcd. for $C_{14}H_{14}N_2O_2P$: 153.0793). Anal. calcd. for $C_{23}H_{39}N_2O_3P$: C 65.36%, H 9.31%, N 6.63%; found: C 65.18%, H 9.70%, N 6.65%.

5-Androsten-17-one (10)



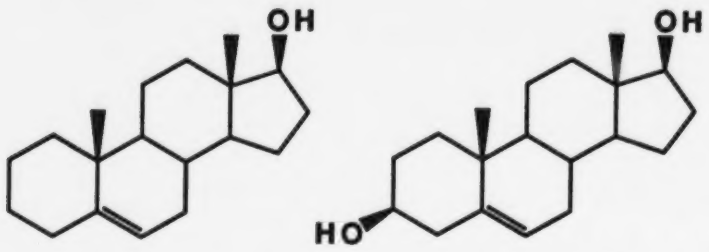
The lithium naphthalenide reduction of compound **9** following LDA deprotonation was not successful, partially due to the presence of diisopropylamine which consumed more that two equivalents of LN. The reaction gave a complex mixture. In another run, a solution of compound **9** (221 mg, 0.525 mmol) in THF (4 mL) was transferred to a suspension of potassium hydride (0.40 g, 35% dispersion in mineral oil, 3.5 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hr to effect complete enolization. A lithium naphthalenide solution (0.72 M, 4 mL, 2.9 mmol) was added. After 1 hr, no starting material could be found on t.l.c.. The reaction mixture was cooled to -78 °C. Water was slowly added to destroy excess potassium hydride. The mixture was allowed to warm up to room temperature and extracted with ether. The extracts were washed with saturated NH_4Cl solution, water and saturated sodium chloride solution successively, dried, filtered and concentrated. Flash column chromatography of the residue on silica gel with gradient elution (ether : Skelly B 5 : 95 to acetone : Skelly B 1 : 3) afforded two compounds. The less polar one was compound **10** (39.1 mg, 26%), identical with the one obtained from Jones oxidation of compound **12**: IR (CH_2Cl_2, cast): 1739 cm^{-1} (st, C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.28 (br, 1H, C**H**=C), 2.55 - 0.8 (m, 21H), 1.02 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); HRMS M^+: 272.2140 (calcd. for $C_{19}H_{28}O$: 272.2140). The second compound was identified as 3β-hydroxy-5-androsten-17-one (7.0 mg, 4%).

17β-Hydroxy-3β-*N,N,N'N'*-tetramethyldiamidophosphoroxy-5-androstene (11)



A solution of $NaBH_4$ (90 mg, 2.37 mmol) in water (0.3 mL) was mixed with a solution of compound **9** (1.00 g, 2.37 mmol) in THF (20 mL). The resulting reaction mixture was stirred at room temperature for 3 hr. Water (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated to give pure compound **11** (0.964 g, 2.27 mmol, 97%). It was further purified by recrystallization from ether - Skelly B to give needle-like crystals: mp 213.5 - 214.5 °C; IR ($CHCl_3$, cast): 3362 cm^{-1} (br, md, hydroxy); ^1H NMR (360 MHz, $CDCl_3$): δ 5.34 (br d, J = 4.7 Hz, 1H, C=C**H**), 4.11 (m, 1H, POC**H**), 3.62 (br t, $J_1 = J_2 = 7.6$ Hz, 1H,), 2.61 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.60 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.35 (br d, J = 7.7 Hz, 2H), 2.1-0.85 (m, 18H), 1.00 (s, 3H, C**H**$_3$), 0.73 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 139.97 (p), 122.30 (ap), 81.86 (ap), 75.20 (d, J = 5.0 Hz, ap), 51.33 (ap), 50.23 (ap), 42.78 (p), 40.32 (d, J = 4.4 Hz, p), 37.09 (p), 36.62 (d, J = 4.1 Hz, ap), 36.61 (p), 31.97 (ap), 31.52 (p), 30.54 (p), 29.87 (d, J = 3.9 Hz, p), 23.48 (p), 20.70 (p), 19.43 (ap), 11.00 (ap); CIMS: 425.5 (M^+ + 1); HRMS: 153.0798 (base peak, calcd. for $C_{14}H_{14}N_2O_2P$: 153.0793). Anal. calcd. for $C_{23}H_{41}N_2O_3P$: C 65.05%, H 9.74%, N 6.6%; found: C 65.06%, H 9.99%, N 6.49%.

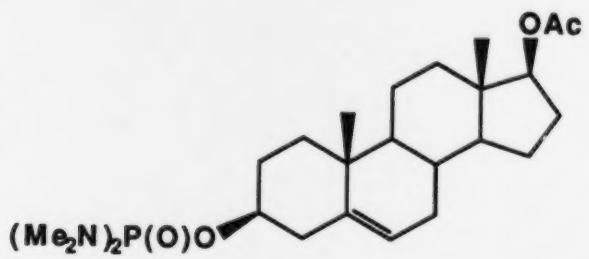
17β-Hydroxy-5-androstene (12) and 3β,17β-dihydroxy-5-androstene (13)



A lithium naphthalenide stock solution (0.71 M, 1.2 mL, 0.85 mmol) was added to compound **11** (67 mg, 0.16 mmol). The resulting blue reaction mixture was stirred at room temperature for 30 min, then quenched with water and extracted with ether (3 x 15 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel with acetone and Skelly B (1 : 6 to 1 : 2) to afford two products. The first one was the reduction product, compound **12** ((32.5 mg, 0.12 mmol, 75%): mp 158.5 - 160.0 °C; IR (CH_2Cl_2, cast): 3253 cm^{-1} (br, md, hydroxyl); ^1H NMR (200 MHz, $CDCl_3$): δ 5.25 (br d, J = 4.2 Hz, 1H, C=C**H**), 3.63 (dd, J_1 = 14 Hz, J_2 = 7.7 Hz, 1H, C**H**OH), 2.3-0.7 (m, 22H), 0.99 (s, 3H, CH_3), 0.74 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): 143.91 (p), 118.71 (ap), 82.04 (ap), 51.53 (ap), 50.80 (ap), 42.79 (p), 40.00 (p), 37.69 (p), 36.74 (p), 32.97 (p), 31.99 (ap),31.55 (p), 30.63 (p), 28.09 (p), 23.52 (p), 22.62 (p), 20.43 (p), 19.58 (ap), 11.03 (ap); HRMS M^+: 274.2299 (calcd. for $C_{19}H_{30}O$: 274.2297). The second product was compound **13** (3.9 mg, 0.013 mmol, 8%) and was identical to the $NaBH_4$ reduction product of 3β-hydroxy-5-androsten-17-one: IR (CH_2Cl_2, cast): 3472, 3374, 3210 cm^{-1} (br, md, hydrogen-bonded hydroxyls); ^1H NMR (360 MHz, $CDCl_3$): δ 5.33 (br d, J = 5.2 Hz, 1H, C=C**H**), 3.63 (dd, $J_1 = J_2$ = 8.1 Hz, 1H, C_{17}**H**OH), 3.50 (m, 1H, C_3**H**OH), 2.3-0.9

(m, 21H), 1.00 (s, 3H, CH_3), 0.74 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 140.73 (p), 120.95 (ap), 81.11 (ap), 70.94 (ap), 51.09 (ap), 50.08 (ap), 42.38 (p), 41.55 (p), 37.04 (p), 36.30 (p), 31.70 (ap), 31.20 (p), 30.84 (p), 29.44 (p), 23.06 (p), 20.39 (p), 18.99 (ap), 10.53 (ap); HRMS M^+: 290.2254 (calcd. for $C_{19}H_{30}O_2$: 290.2246).

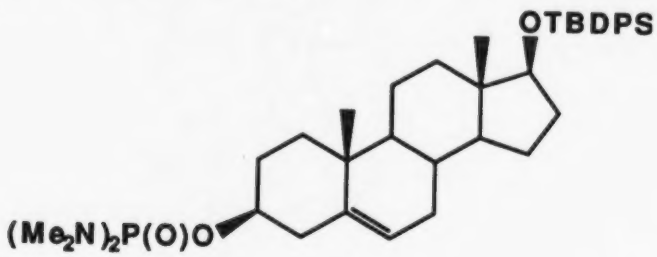
17β-Acetoxy-3β-*N,N,N'N'*-tetramethyldiamidophosphoroxy-5-androstene (14)



Compound **11** was dissolved in a mixture of ether (5 mL) and pyridine (5 mL). This solution was cooled to 0 °C with an ice-bath and acetic anhydride (5 mL) was added. The reaction mixture was stirred at room temperature under argon overnight. All the solvents, reagents and acetic acid produced were distilled off with a rotary evaporator connected to a dry ice condenser and a water aspirator. The crude solid residue was chromatographed on silica gel with acetone : Skelly B (1 : 6) to give compound **14** (410 mg, 0.88 mmol, 98%): mp 174.5 - 175.0 °C (needle-like crystals from ether - Skelly B); IR ($CHCl_3$, cast): 1734 cm^{-1} (st, C=O, ester); ^1H NMR (360 MHz, $CDCl_3$): δ 5.34 (br d, J = 4.3 Hz, 1H, C=C**H**), 4.57 (dd, J_1 = 9.1 Hz, J_2 = 7.8 Hz, 1H, C**H**OAc), 4.09 (m, 1H, POC**H**), 2.61 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.60 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.35 (d, J = 7.7 Hz, 2H), 2.2-0.85 (m, 17H), 2.01 (s, 3H, CH_3CO_2-), 0.99 (s, 3H, CH_3), 0.77 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 171.23 (p), 139.92

(p), 122.20 (ap), 82.81 (ap), 75.30 (d, J = 4.4 Hz, ap), 51.00 (ap), 49.98 (ap), 42.40 (p), 40.23 (d, J = 4.4 Hz, p), 36.99 (p), 36.76 (p), 36.57 (d, J = 4.1 Hz, ap), 36.56 (p), 31.73 (ap), 31.47(p), 29.79 (d, J = 7.1 Hz, p), 27.58 (p), 23.61 (p), 21.19 (ap), 20.55 (p), 19.39 (ap), 11.96 (ap); CIMS: 467.3 ($M^+ + 1$); HRMS: 465.2871 (calcd. for $M^+ - 1$: 465.2881), 153.0799 (base peak, calcd. for $C_4H_{14}N_2O_2P$: 153.0792).

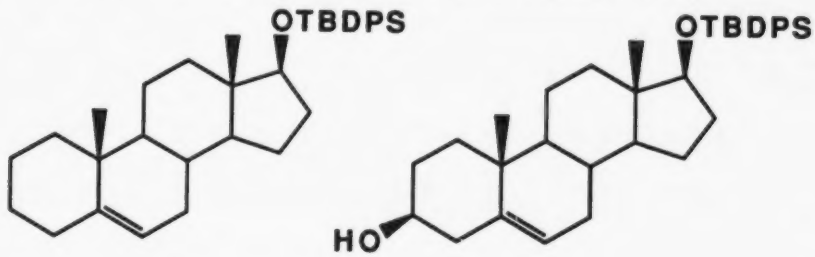
17β-*tert*-Butyldiphenylsiloxy-3β-*N,N,N'N'*-tetramethyldiamido-phosphoroxy-5-androstene (15)



t-Butyldiphenylsilyl chloride (1.4 mL, 1.5 mmol) was added to a solution of compound **11** (417 mg, 0.982 mmol) and imidazole (330 mg, 4.9 mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred at room temperature under argon for 24 hr. Water (10 mL) was added and the resulting mixture was stirred at room temperature for 1 hr and extracted with ether (3 x 20 ml). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. The residue was chromatographed on silica gel with acetone-Skelly B (1 : 6) to afford compound **15** (0.618 g, 95%): IR (CH_2Cl_2, cast): 1226 (st, P=O), 1139 (st, C-O, ester), 1089 (st, C-O), 992 cm^{-1} (st, P-O); ^1H NMR (360 MHz, $CDCl_3$): δ 7.63 (m, 4H, phenyl), 7.35 (m, 6H, phenyl), 5.30 (d, J = 5.1 Hz, 1H, C=C**H**CH_2), 4.09 (m, 1H, POC**H**), 3.61 (dd, J_1 = J_2 = 8.3 Hz, 1H, SiOC**H**), 2.61 (d, J = 9.9 Hz, 6H, NC**H**$_3$), 2.60 (d, J = 9.9 Hz, 6H,

NCH_3), 2.34 (br d, J = 8.0 Hz, 1H), 1.95 - 0.83 (m,), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.99 (s, 3H, 10-CH_3), 0.84 (s 3H, 17-CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 139.86 (p), 136.00 (ap), 135.96 (ap), 134.96 (p), 134.45 (p), 129.47 (ap), 129.41 (ap), 127.40 (ap), 127.35 (ap), 122.30 (ap), 82.49 (ap), 75.15 (d, J = 4.8 Hz, a), 50.53 (ap), 50.13 (ap), 43.49 (p), 40.27 (d, J = 4.4 Hz, p), 37.01 (p), 36.84 (p), 36.57 (d, J = 3.5 Hz, a), 36.52 (p), 31.94 (a), 31.45 (p), 30.78 (p), 29.83 (d, J = 3.9 Hz, p), 27.09 (ap), 23.58 (p), 20.73 (p), 19.38 (ap), 19.35 (p), 11.60 (ap); CIMS: 663.5 (M^+ + 1) and 664.5 (M^+ + NH_3 + 1). Anal. calcd. for $C_{39}H_{59}N_2O_3PSi$: C 70.65%, H 8.98%, N 4.23%; found: C 70.27%, H 9.34%, N 4.18%.

17β-*tert*-Butyldiphenylsiloxy-5(6)-androstene (16) and 17β-*tert*-butyldiphenylsiloxy-3β-hydroxy-5(6)-androstene (17)

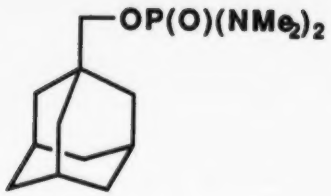


16 17

A lithium naphthalenide solution (0.72 M, 1.0 mL, 0.72 mmol) was added to compound **15** (87 mg, 0.131 mmol). The reaction mixture was stirred at room temperature under argon for 30 min, quenched with saturated NH_4Cl solution and extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution, dried, filtered and concentrated. The residue was subjected to flash chromatography with acetone and Skelly B (0 : 100 to 1 : 6) to afford two products. The first compound was the reduction product,

compound **16** (45.20 mg, 0.88 mmol, 67%): mp 82.5 - 84.0 °C; IR (CH_2Cl_2, cast): 1090 cm^{-1} (st, C-O); ^1H NMR (360 MHz, $CDCl_3$): δ 7.65 (m, 4H, phenyl), 7.34 (m, 6H, phenyl), 5.21 (br d, J = 5.3 Hz, 1H, C=C**H**), 3.61 (pseudo t, J = 5.3 Hz, 1H, C**H**OSi), 2.10 (m, 1H), 1.92 (m, 2H), 1.75 (m, 3H), 1.47 (m, 10H), 1.18 (m, 2H), 1.06 (s, 9H, *tert*-butyl), 0.98 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.80 (m, 3H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 143.84 (p), 136.08 (ap), 136.04 (ap), 135.09 (p), 135.04 (p), 129.48 (ap), 129.43 (ap), 127.44 (ap), 127.39 (ap), 118.77 (ap), 82.63 (ap), 50.78 (ap, two peaks in C_6D_6 at 51.03 and 50.79), 43.55 (p), 39.97 (p), 37.67 (p), 37.04 (p), 32.95 (p), 31.97 (ap), 31.54 (p), 30.87 (p), 28.31 (p), 27.14 (ap), 23.65 (p), 22.62 (p), 20.50 (p), 19.55 (ap), 19.42 (p), 11.68 (ap); HRMS M^+: 512.3475 (calcd. for $C_{35}H_{48}OSi$: 512.3475). The second product was compound **17** (6.10 mg, 0.012 mmol, 9%): IR (KBr): 3346 cm^{-1} (br, md, -OH); ^1H NMR (360 MHz, $CDCl_3$): δ 7.65 (m, 4H, phenyl), 7.34 (m, 6H, phenyl), 5.28 (br d, J = 5.3 Hz, 1H, C=C**H**), 3.61 (pseudo t, J = 5.3 Hz, 1H, C**H**OSi), 3.46 (m, 1H, HOC**H**), 2.23 (m, 2H), 1.78 (m, 4H), 1.40 (m, 10H), 1.20 (m, 2H), 1.05 (s, 9H, *tert*-butyl), 0.98 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.80 (m, 3H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 140.88 (p), 136.08 (ap), 136.03 (ap), 135.04 (p), 134.56 (p), 129.50 (ap), 129.45 (ap), 127.44 (ap), 127.40 (ap), 121.50 (ap), 82.57 (ap), 71.81 (ap), 50.69 (ap), 50.31 (ap), 43.56 (p), 42.36 (p), 37.34 (p), 36.95 (p), 36.63 (p), 32.04 (ap), 31.72 (p), 31.53 (p), 30.84 (p), 27.14 (ap), 23.65 (p), 20.83 (p), 19.47 (ap), 19.42 (p), 11.63 (ap); HRMS M^+: 527.3321 (calcd. for $C_{35}H_{47}O_2Si$: 527.3345).

***N,N,N'N'*-Tetramethyldiamidophosphoroxymethyladamantane (18)**



n-Butyllithium in hexanes (1.6 M, 5.7 mL, 9.1 mmol) was added dropwise to a solution of adamantylmethanol (1.163 g, 7.00 mmol) in DME - TMEDA (4 : 1, 20 mL) at -78 °C under argon. The solution was allowed to warm up to room temperature and stirring was continued for another 20 min. TMDAPC (90%, 3.5 mL, 21 mmol) was added. The reaction mixture was stirred at room temperature under argon overnight. Water (10 mL) was added and stirring was continued for another 10 min before extraction with ether (3 x 30 mL). The extracts were washed with saturated sodium chloride solution three times, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel with acetone - Skelly B (1 : 6) to afford compound **18** (1.637 g, 5.45 mmol, 78%): mp 69.5 - 70.5 °C; IR (CH_2Cl_2, cast): 1260 (st, P=O), 942 cm^{-1} (st, P-O); ^1H NMR (360 MHz, $CDCl_3$): δ 3.42 (d, J = 4.4 Hz, 2H, CH_2OP), 2.62 (d, H = 9.6 Hz, 12H, $PNCH_3$), 1.95 (br s, 3H, CH at bridgehead), 1.70 (br d, J = 12.2 Hz, 3H, $CHCH_2CH$), 1.61 (br d, J = 12.2 Hz, 3H, $CHCH_2CH$), 1.52 (d, J = 2.6 Hz, 6H, $CHCH_2C$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 74.52 (d, J = 5.2 Hz, p), 39.17 (p), 37.06 (p), 36.69 (d, J = 3.9 Hz, ap), 33.91 (d, J = 7.9 Hz, p), 28.11 (ap); HRMS M^+: 300.1963 (calcd. for $C_{15}H_{29}N_2O_2P$: 300.1966).

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